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TUBEROUS SCLEROSIS

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A number of features of tuberous sclerosis of the brain make a study of the condition most engrossing—its relative infrequency, its clinical forms, its association with anomalies elsewhere, its roentgenographic peculiarities and its evolutionary problems. We have studied 25 cases of the disease, 3 with autopsy data, and shall discuss a few of these points.

In 1863 von Recklinghausen [1] observed sclerotic areas in the brain and myomas in the heart of an infant. It was not until 1880, however, that Bourneville [2] described the syndrome constituting tuberous sclerosis. He demonstrated sclerotic areas in the brain of an underdeveloped girl with epilepsy, idiocy, hemiplegia and "acne rosacea." In 1908 Vogt [3] delineated the classic symptom triad of tuberous sclerosis, namely, idiocy, epilepsy and adenoma sebaceum. Since then many cases of "Bourneville's disease" have been reported and various theories advanced to explain its genesis. Sherlock [4] suggested that the condition be designated "epiloia."

This unusual disease is congenital and may be hereditary or familial. There is often evidence of neuropathic defects in the patient's family. Fabing [5] reported the occurrence of the condition in both members of a pair of identical twins whose cutaneous lesions were mirror images of each other, and Hopwood [6] described it in one of nonidentical twins. Its occurrence through three generations of one family has been reported by Kirpicznik [7] and by Quill and Marting.[8] Van Bouwdijk Bastiaanse and Landsteiner [9] encountered it in 5 of 9 siblings.

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2. Bourneville, D.: Scléreuse tubéreuse des circonvolutions cérébrales: idiotie et épilepsie hémiplégique, Arch. de neurol. **1**:81, 1880.
3. Vogt, H.: Zur Pathologie und pathologischen Anatomie der verschiedenen Idiotieformen: II. Tuberöse Sklerose, Monatschr. f. Psychiat. u. Neurol. **24**:106, 1908.
4. Sherlock, E. B.: The Feeble-Minded, London, The Macmillan Company, 1911, pp. 241-243.
5. Fabing, H.: Tuberous Sclerosis with Epilepsy in Identical Twins, Brain **57**:227 (Oct.) 1934.
6. Hopwood, A. T.: Tuberous Sclerosis: Report of Five Cases, Including One Case in One of Twins, Ohio State M. J. **33**:277 (March) 1937.
7. Kirpicznik, J.: Ein Fall von tuberoser Sklerose und gleichzeitigen multiplen Nierengeschwülsten, Virchows Arch. f. path. Anat. **202**:358, 1910.
8. Quill, L. M., and Marting, E. C.: Epiloia, Surgery **9**:581-590 (April) 1941.
9. van Bouwdijk Bastiaanse, F. S., and Landsteiner, K.: Eine familiäre Form tuberoser Sklerose, Zentralbl. f. d. ges. Neurol. u. Psychiat. **32**:197, 1923.

Tuberous sclerosis has seemed to be much less prevalent in this country than in Europe, where its incidence is approximately 0.6 per cent in institutions for epileptic and feebleminded patients. Reports published in this country indicate that its incidence varies from 0.1 to 0.5 per cent in similar institutions.

While the basic characteristics of tuberous sclerosis are developmental anomalies in tissues of ectodermal origin, particularly the brain, skin and retina, defective development and tumor formation are not infrequently manifested elsewhere. The kidney, heart, adrenal, liver, thyroid, lung and ovary are sites of such involvement. Hyman [10] stated that renal tumors of mixed embryonal type occur in 80 per cent of cases of tuberous sclerosis. They are described as being generally multiple and bilateral, of variable size, nearly always cortical and rarely, if ever, forming metastases. In addition to frank tumor formation, various stigmas of degeneracy are frequently seen, such as harelip, high palate, myopia, spina bifida, polydactylism and congenital heart disease.

The usual clinical criteria for the recognition of tuberous sclerosis are adenoma sebaceum on the face, retinal tumors, mental deficiency and convulsions, although it is not necessary for all these qualifications to be fulfilled in order that the diagnosis be established. At times sebaceous adenomas are the only sign of the disorder. Involvement of the nervous system in the form of mental deficiency and either generalized or localized convulsions is paramount but not invariable. Occasionally tumors of the viscera occupy the foreground and relegate the involvement of the skin and nervous system to a position of less prominence. The disease may manifest itself in infancy, or not until many years later. Thus, Stewart [11] reported its occurrence in a 21 year old woman with normal intelligence and no cutaneous or visceral tumors, who, until the attack in which she died, had never had a convulsion. It can be seen, therefore, that the clinical picture is subject to rather gross variations.

The cutaneous involvement usually takes the form of adenoma sebaceum, which may be a true tumor of the sebaceous glands, but most frequently consists of circumscribed hypertrophy of these structures. The lesions vary in size from that of a pinhead to that of a split pea; they are yellowish or pinkish, are usually distributed in a butterfly pattern over the nose, cheeks and nasolabial folds, are benign and persist indefinitely. They are almost never seen below the level of the clavicles. They usually appear in early childhood or at puberty. Other types of cutaneous manifestations are pedunculated polyps, subcutaneous nodules, pigmented nevi, café au lait spots, filiform papillomas of the nail beds and "shagreen skin" over the lumbosacral area. The dermatologic aspects of tuberous sclerosis have been admirably reviewed by Butterworth and Wilson Jr.[12]

The retinal lesions, as a rule, consist of tumors (phakomas) which may be single or multiple, flat or raised, whitish gray nodules, situated anywhere on the fundus, and which ordinarily are not directly connected with blood vessels. They sometimes contain cysts, which may rupture or become malignant. Van der Hoeve [13] reported having witnessed tumor buds floating in the vitreous to other parts of the retina.

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10. Hyman, A.: The Association of Hypernephroma with Tuberose Brain Sclerosis and Adenoma Sebaceum, J. Urol. **8**:317 (Oct.) 1922.

11. Stewart, R. M.: An Atypical Form of Tuberous Sclerosis, Brit. M. J. **2**:60 (July 13) 1935.

12. Butterworth, T., and Wilson, McC., Jr.: Dermatologic Aspects of Tuberous Sclerosis, Arch. Dermat. & Syph. **43**:1-41 (Jan.) 1941.

13. van der Hoeve, J.: Eye Symptoms in Phakomatosis: The Doyne Memorial Lecture, Tr. Ophth. Soc. U. Kingdom **52**:380, 1932.

While the vast majority of patients with this disease are mentally deficient, instances have been recorded in which the mentality has been normal, or only slightly below normal. The patient is usually slow in learning to walk, talk and comprehend. Sometimes he is apathetic, excitable and negativistic or assumes bizarre postures or stereotyped movements. Critchley and Earl [14] described the psychologic status of epiloia as a combination of intellectual defect and a psychosis resembling a primitive type of schizophrenia.

Neurologic examination may or may not show evidences of a focal lesion. Occasionally tumors are so situated as to produce an increase in intracranial pressure.

A few roentgenographic alterations have been described as occurring with the disease. Gottlieb and Lavine [15] reported thickening of the tables of the skull and a peculiar mottling, with indistinct islands of increased density alternating with areas of rarefaction. Roentgenograms of the hands and feet have shown periosteal thickening and generalized osteoporosis of the metacarpal and metatarsal bones and their phalanges, fragmentation of the cortical layers and a few areas of rarefaction, suggesting small cysts. Pancoast, Pendergrass and Schaeffer [16] said that "not infrequently the bones of the extremities and occasionally of the calvaria show changes which include periosteal deposits and cystic or 'punched out' areas in the spongiosa." They pointed out that the calcified lesions of tuberous sclerosis may be confused with calcifications in the choroid plexuses or the pineal body or with other calcifications. Yakovlev and Corwin [17] reported the roentgenographic demonstration of multiple discrete areas of calcification scattered through the brain and attributed them to degenerative changes in the tuberous nodules. Hall [18] described irregular areas of increased density in the skull and dilatation of the venous channels.

Pneumographic studies of the brain may or may not reveal a pathologic condition. Not infrequently the ventricular system is dilated and tumors of the lateral ventricles can be demonstrated.

Pathologically, tuberous sclerosis forms a clearcut entity. The surface of the brain presents firm, smooth, flattened, pale nodules, varying in size, shape, number and distribution. However, the configuration of the gyri and sulci is not disturbed. Similar foci may occur in the subcortical white matter. Into the lateral ventricles, particularly from the floor, may protrude subependymal tumor nodules, giving the appearance of "candle gutterings," which, by obstruction, sometimes cause an increase in intracranial pressure. The ventricles, while occasionally normal in size, are usually enlarged.

Microscopic examination discloses considerable disturbance in cortical cytoarchitecture. The molecular layer is broadened; Cajal cells may be numerous, and the pyramidal cells are diminished in number. Scattered through the cortex, and to a much less extent through the white matter, are fantastically formed giant nerve cells, which vary in size, contour, location and orientation. The enlargement involves the whole cell—body, nucleus, axon and dendrites. Degenerative changes are seen in a few such cells. There occur, also, hyperplasia and hypertrophy of glial elements in the gray and white matter, so that monster astrocytes are seen

14. Critchley, M., and Earl, C. J. C.: Tuberose Sclerosis and Allied Conditions, Brain **55**:311 (Sept.) 1932.

15. Gottlieb, A. S., and Lavine, G. R.: Tuberous Sclerosis with Unusual Lesions of the Bones, Arch. Neurol. & Psychiat. **33**:379 (Feb.) 1935.

16. Pancoast, H. K.; Pendergrass, E. P., and Schaeffer, J. P.: The Head and Neck in Roentgen Diagnosis, Springfield, Ill., Charles C Thomas, Publisher, 1940, p. 663.

17. Yakovlev, P. I., and Corwin, W.: A Roentgenographic Sign in Cases of Tuberous Sclerosis of Brain (Multiple "Brain Stones"), Arch. Neurol. & Psychiat. **42**:1030 (Dec.) 1939.

18. Hall, G. S.: Tuberose Sclerosis, Rheostosis, and Neurofibromatosis, Quart. J. Med. **9**:1 (Jan.) 1940.

singly or in clusters. Oligodendroglia cells are multiplied. The glial elements and the cytoplasm of the diseased ganglion cells contain a considerable increase in heat-resistant mineral ash, composed particularly of calcium oxide.[19] In the sclerotic areas there is either patchy or confluent destruction of myelin sheaths. Fat particles are seen in the microglia and oligodendroglia cells and in the perivascular spaces. The smaller blood vessels show thickening of the intima. The subependymal tumors are mostly made up of primitive glia cells. Small deposits of calcium may be present in the tuberous nodules and in the intraventricular masses.

On the whole, the cerebellum is said not to be as severely involved as the cerebrum. Wertham [20] noted pathologic glia cells, with ill defined protoplasm and irregular, dissimilar nuclei, in the spinal cord; these differed from the cells seen in cases of Recklinghausen's disease.

The varying opinions concerning the genesis of tuberous sclerosis have been admirably summarized by Globus,[21] who divided them into two main schools. The first maintains that the disease is an expression of disordered development, having its incipience in the early embryonic life of the person affected, and that it is associated with abnormal proliferative tendencies in certain elements in the central nervous system and in other organs. The disease thus acquires a blastomatous character.

This school contends that the malformed cells are neuroblasts and spongioblasts which, having been released from normal restraints, and by virtue of the inherent force of self differentiation, have grown into monster cells. The disturbance of cytoarchitecture is considered to be the result of impairment of the cellular capacity for proper orientation. Heterotopias in extracortical areas presumably result from an arrest in normal migration of the cells toward the cortex. The subependymal tumors are regarded as the outcome of imbalance of cell growth, with release of proliferative tendencies. Wertham expressed the belief that the developmental disorganization occurs between the fifth and the sixth fetal month, in the last phase of the wandering of the neuroblasts to the cortex; hence the lack of disturbance of the cerebral topography.

The second school regards the disease as primarily neoplastic, the causative factor being inherent in the cell elements of the organ from its incipiency and the process slowly progressive during the histogenetic and ontogenetic stages of development, with resulting defective development. To this school belong Ferraro and Doolittle,[22] who found little to support the concept of a basic malformation. They attributed the disturbed cytoarchitecture to a process of glial replacement of nerve cell elements undergoing progressive and degenerative changes. They contended that the monster nerve cells are the result of unknown stimuli provoking hypertrophy of the cellular structures, and that reactive manifestations of the astrocytes leading to the formation of monster glia cells are observed in connection with other degenerative and neoplastic processes. The occasional presence of nodules of unquestionable neoplastic nature in the inner cortical layers and the association of tuberous sclerosis with tumor of the brain in the same patient are, in their

19. Alexander, L., and Myerson, A.: Cell Minerals in Amaurotic Idiocy, Tuberous Sclerosis and Related Conditions, Studied by Microincineration and Spectroscopy, Am. J. Psychiat. **96**:77 (July) 1939.

20. Wertham, F., and Wertham, F.: The Brain as an Organ, New York, The Macmillan Company, 1934, p. 412.

21. Globus, J. H.: Malformation in the Central Nervous System, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1150.

22. Ferraro, A., and Doolittle, G. J.: Tuberous Sclerosis (Diffuse Neurospongioblastosis), Psychiatric Quart. **10**:365 (July) 1936.

opinion, further points emphasizing the primarily neoplastic nature of the disease. That the stimulus to neoplasia must still be active after birth seems, to them, to be evidenced by the microglial reaction and the occurrence of demyelination, with fatty products of degeneration. They postulate that the anomalies encountered in other organs, such as the kidney and the heart, may be a consequence of pathologic changes in some of the most important cerebral regulating centers.

There are some other disorders that are considered to have a close genetic alliance with tuberous sclerosis. Thus, under the classification of "congenital ectodermoses," Yakovlev and Guthrie [23] included tuberous sclerosis, neurofibromatosis and encephalotrigeminal angiomatosis. They expressed the belief that all three disorders have their origin in malformation of the ectoblast and that they differ in the period of embryogenesis at which the disturbance occurs, in the predominance of one or another of the ectodermal structures involved and in the degree of participation of mesodermal elements. By some investigators Hippel-Lindau disease is included. To this group of disorders Hall added rheostosis, a condition of the extremities in which there are hyperostosis, fibrocystic changes, subperiosteal areas suggestive of cyst formation and overgrowth of periosteal bone.

There is no specific treatment for tuberous sclerosis. Anticonvulsant medication may or may not ameliorate the seizures. If intracranial hypertension exists, relief may result on the removal of obstructing intraventricular nodules. Friedman [24] reported the cessation for at least two and a half years of convulsions in a girl treated with radiation to the head, 1,700 r being given in divided doses.

The clinical material from which this paper is derived is based on the study of 25 patients. Twenty-two were admitted to the Caro State Hospital for Epileptics, and 3 patients were seen by one of us (A. T. R.) at the Indiana University Medical Center. In all but 1 instance (case 13) hospitalization was sought because of the presence of convulsions and mental deficiency. Patients were not accepted for hospitalization because of the presence of tuberous sclerosis alone, although 1 patient already committed and awaiting admission was admitted somewhat earlier than she otherwise would have been, when her parents brought her to the institution and urged her early admission. All patients were selected for this study because of the presence of the characteristic facial lesions.

PRESENT STUDY

CLINICAL CONSIDERATIONS

Etiologic Factors.—Incidence: Data are not available regarding the prevalence of this condition at the Indiana University Hospitals. At the Caro State Hospital the diagnosis of tuberous sclerosis has been made in the cases of 22 of 3,940 newly admitted patients, an incidence of 0.56 per cent.

Sex: Fifteen patients were males and 10 were females.

Age: The youngest patients (2) were 3 years old (age at admission); the oldest was 41 years of age. The distribution by age groups was as follows: 1 to 4 years, 5 patients; 5 to 9 years, 9 patients; 10 to 14 years, 4 patients; 15 to 19 years, 5 patients, and 35 to 45 years, 2 patients. The average age was 11.7 years.

Race: All but 1 of our patients were of the white race. This patient, a boy of 3 years, was the illegitimate son of a white father and a mother who was a

23. Yakovlev, P. I., and Guthrie, R. H.: Congenital Ectodermoses (Neurocutaneous Syndromes) in Epileptic Patients, Arch. Neurol. & Psychiat. **26**:1145 (Dec.) 1931.

24. Friedman, A. B.: Tuberous Sclerosis: Relief of Epileptic Symptoms by Radiation Therapy, Arch. Neurol. & Psychiat. **41**:565 (March) 1939.

full-blooded American Indian. Another patient, a girl now about 19 years old, was abandoned in her infancy by a tribe of gypsies, and her appearance was strongly suggestive of that people. One girl was the daughter of Austrian Jewish parents.

Heredity: Two of our patients (cases 11 and 18) were members of a large family group which showed several variations of the neurocutaneous syndrome or congenital ectodermoses. The genealogic table (fig. 1) and the accompanying notes summarize the significant data on this family.

The following data on our series, other than those included in figure 1, are presented for the sake of completeness:

1. No patient was a child of a parent with tuberous sclerosis.

2. Only 1 patient was a child of a parent with a convulsive disorder. Two of this patient's 4 siblings were retarded mentally, and the other parent, the father, had served at least two prison sentences.

3. One patient had 2 feebleminded sisters.

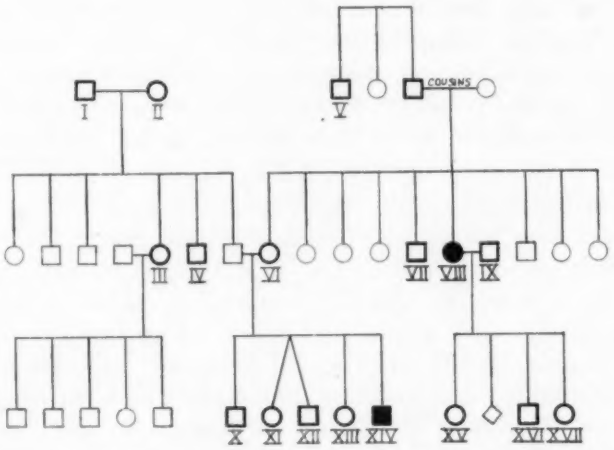

Fig. 1.—Genealogic chart for a family showing several variations of the neurocutaneous syndrome.

I and *II*, paternal grandfather and grandmother of patient 11 (*XIV*). The grandfather was intemperate and indulged in periodic sprees of several days' duration. The grandmother is subject to grand mal attacks, which recur regularly.

III, paternal aunt of patient 11. She suffers from migraine and on one occasion was discharged from the psychopathic ward of a general hospital with a diagnosis of "acute reactive hysterical reaction."

IV, paternal uncle of patient 11. This man was heavily alcoholic until his death, at the age of 37, which was caused by pulmonary tuberculosis.

V, maternal great-uncle of patient 11 and uncle of patient 18. This man was also heavily alcoholic.

VI, mother of patient 11 and sister of patient 18. This woman was seen at the dermatology clinic of Harper Hospital, Detroit, in 1932, because of an eruption of the face and feet of ten years' duration. The diagnosis, confirmed by biopsy, was fibrous papilloma (Recklinghausen's disease). Roentgenograms of the hands and feet showed changes in bone, involving the heads of the distal phalanges of the small and ring fingers of the right hand and the distal phalanges of the great toes. The process was a little more pronounced about the right great toe and was considered to be entirely secondary to the erosion of bone by the papillomatous growth. She was admitted to the University Hospital, Ann Arbor, Mich., in 1933 with a history of blindness, attacks of unconsciousness and headaches of four months' duration. There were multiple cutaneous lesions over the chin, the alae of the nose and the chest. Scattered

(Legend Continued on following page)

4. One patient had a maternal uncle who had had jacksonian attacks for several years after an injury to the head. Another patient had a maternal aunt who suffered from typically grand mal convulsions.

5. One patient had several relatives who exhibited lesions about the eyelids which had been diagnosed by several dermatologists as xanthoma.

6. One patient was a member of a pair of nonidentical twins, the other twin being entirely normal.

Age of Mother at Birth: For 6 patients the age of the mother at the time of birth was unknown or was not given. For the remaining patients the age distribution of the mothers was as follows: 15 to 19 years, 1; 20 to 24 years, 7; 25 to 29 years, 4; 30 to 34 years, 3, and 35 to 39 years, 4.

Order of Birth: For 5 patients the order of birth was unknown. Table 1 shows the distribution of the remaining 20 patients.

Trauma: 1. Birth trauma: There were no recorded instances of dystocia, precipitate labor or forceps delivery in our series of patients. Neither was there any case of serious illness or injury to the mothers during pregnancy.

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elsewhere over the body were firm, whitish or yellowish nodules, varying from a pinhead to a bean in size. Ventriculographic studies demonstrated a tumor in the suprasellar region, arising apparently from the septum pellucidum and invading the inferior walls of both lateral ventricles. At operation (Dr. Max Peet) a large, partially intraventricular tumor, possibly arising from the septum pellucidum, was apparently completely removed from the subfrontal region. The histologic diagnosis was glioblastoma multiforme.

VII, brother of patient 18 and uncle of patient 11. This boy was admitted to the Lapeer (Mich.) State Home and Training School as an epileptic patient at the age of 12 years. At birth he had a "nevus on the right cheek," which grew steadily. Convulsions began on the third day of life and recurred irregularly, approximately once each month. He could neither feed nor dress himself and was untidy in his toilet habits. Unfortunately, there is no detailed record of the physical examination, and no roentgenographic studies were made. He died in the institution, at the age of 13. The cause of death is unknown.

VIII, patient 18 in this series.

IX, husband of patient 18, a man of low intelligence. He has a record of six previous arrests on charges ranging from breaking and entering to statutory rape. At present he is serving his third prison sentence, the charge being desertion and nonsupport.

X and XIII, siblings of patient 11. These children are residents of the Wayne County Training School, Northville, Mich.; their intelligence quotients are 48 and 62 respectively. Both are said to have had convulsions, but none has been evident during their institutional residence.

XII, sibling of patient 11. This boy is also feebleminded, his intelligence quotient being 48. He suffers frequent petit mal attacks.

XI, the twin sister of XII. She was admitted to the Caro State Hospital for Epileptics in 1935, when she was 4 years of age. Seizures began at the age of 4 months. She never developed properly and at the time of admission was unable even to hold her head erect. There were no cutaneous lesions and no unusual neurologic signs. A pneumoencephalogram showed far advanced generalized atrophy or hypoplasia of the brain. She died in status epilepticus one month after admission. Autopsy was not performed.

XIV, patient 11 in our series.

XV and XVII, children of patient 18, cousins of patient 11. These children are confined at the Lapeer (Michigan) State Home and Training School. Physical examinations revealed nothing of significance in either. Both are in the imbecile range of intelligence. Neither has ever suffered convulsions, and adenomas are not present on their faces.

XVI, brother of XV and XVII. This boy, in all likelihood, is also feebleminded, although formal tests have never been given. He presents a behavior problem, and it is growing increasingly difficult to find a boarding home for him because of his untidiness.

Although the information available on patient VII leaves much to be desired, it is probable that patients VI, VII, VIII and XIV represent the occurrence of all three variations of the neurocutaneous syndrome within a single family group.

2. Postnatal trauma: Three patients had a history of postnatal trauma of such severity as to be a possible precipitating factor in the convulsive disorder. A girl at the age of 30 months was thrown to the sidewalk while playing and suffered a momentary loss of consciousness. Three months later she had her first convulsion. A second girl fell from her high chair at the age of 11 months and suffered a severe laceration of the scalp. Within a month she had her first convulsion. A man had had "worm fits" at the age of 2½ years. He received a severe beating about the head in a school fight at the age of 8 years. After this he underwent

TABLE 1.—*Distribution with Respect to Order of Birth of Twenty Patients with Tuberous Sclerosis*

Order of Birth	Number of Children in Family								
	1	2	3	4	5	6	7	10	12
1	2	3	..	..	2	..	..	..	..
2	..	..	1	..	1	..	..	..	..
3	..	..	1	..	1	1	..	..	..
4	..	..	..	1	..	1	..	..	..
5	..	..	..	..	..	..	..	1	..
6	..	..	..	..	..	1	1	..	..
7	..	..	..	..	..	..	1	..	..
11	..	..	..	..	..	..	..	..	1
12	..	..	..	..	..	..	..	..	1

TABLE 2.—*Distribution of Twenty-Five Patients with Tuberous Sclerosis with Respect to Ages at Appearance of Symptoms*

Age at Onset of Convulsions	Number	Intelligence Quotient				Age at Appearance of Adenoma Sebaceum No.
		0-25	26-50	51-75	Over	
Under 1 year	17	15	1	1	..	Unknown 9 2 years 2 5 years 1 7 months 1 2 years 3 6 years 1
1 to 4 years	4	1	1	1	1*	Unknown 3 11 years 1
5 to 9 years	2	1	..	1	..	Unknown 1 Infancy 1
10 to 14 years	1	..	..	1	..	14-15 years 1
20 to 24 years	1	..	..	..	1	38 years 1
Totals	25	17 (68%)	2 (8%)	4 (16%)	2 (8%)	

* A girl, normal at the age of 5 years, had deteriorated into a helpless idiot at her death, at the age of 19.

conspicuous changes in personality. At the age of 22 he fell from a ladder and within a few hours experienced his first grand mal attack.

Inflammation: No patient in our series had a history of inflammation of the central nervous system which seemed to be of etiologic significance in the precipitation of the convulsive disorder.

Syphilis: For every patient the Kahn reactions of the blood serum and the spinal fluid were negative.

Symptoms.—The ages at the onset of convulsions, the intelligence quotients and the ages at the appearance of the lesions of adenoma sebaceum are summarized in table 2. For 13 patients the age at the appearance of the characteristic sebaceous adenomas was unknown. In only 1 of the remaining patients did the appearance of the facial lesions definitely antedate the onset of convulsions.

Every patient in the series had the grand mal type of attack at the time of admission. Five patients suffered petit mal attacks as well; in 2 of these the minor attacks were present two and twelve years respectively before the major attacks made their appearance. The frequency of the grand mal attacks varied from one every four months to eight a week. Eleven of the 25 patients had frequent bouts of serial seizures and status epilepticus.

Physical and Neurologic Observations.—The results of the general physical and neurologic examination of the patients in this series, other than those indicated under the systems discussed later, showed surprisingly few variations from normal. Many of the patients were helpless idiots and presented evidence of general underdevelopment and malnutrition. In most instances subjective signs and symptoms were of little or no value.

One patient had congenital equinovarus of the right foot, and another had eversion of both feet, so that she walked on the inner aspects, which were thickly calloused. One patient had a very protuberant abdomen, due to megacolon, the presence of which was confirmed by roentgenographic studies after a barium sulfate enema. One patient had a large congenital ventral hernia due to severe diastasis recti, which was successfully operated on after her admission to the hospital.

In 1 patient right spastic hemiparesis, which persisted throughout her lifetime, developed at the time of her first convulsion. She also had a bifid uvula. Another patient suffered hemiparesis of three days' duration after a seizure. One patient had signs of a mild lesion of the pyramidal tract in both lower extremities. One patient showed alternating convergent strabismus, with nystagmus on deviation of the eyeballs in any direction and on attempted fixation. Bilateral keratoconus and unilateral posterior polar cataract, to be described later, were present in another patient. One patient was found to be hemophilic.

In 1 patient (case 21) routine roentgenographic examination of the chest on admission (Michigan Department of Health) showed "definite enlargement of the heart, apparently involving primarily the right side of the heart, very possibly the right auricle in particular. The cardiac apex was not displaced. The aorta was clearly visible. The pulmonary vessels on the left side at least appeared normal. A lesion of the tricuspid valve might produce an appearance of this sort. It is also conceivable that the shadow to the right, which so closely resembled the right border of the heart, may, in fact, have been some other structure in the mediastinum." Fluoroscopic examination at the University Hospital, Ann Arbor, Mich., showed that the heart was obviously not enlarged. The secondary shadow, which extended well beyond the heart to the right, did not pulsate. It was best seen when the patient was rotated with the right side forward, an indication of its far posterior position. With the patient in the direct lateral position the mass was seen to be deep in the paravertebral gutter on the right side. Its margins were clearly defined and regular. It did not appear to be pedunculated. Electrocardiograms, including tracings from serial precordial leads, were well within normal limits. Subsequent fluoroscopic examinations and single flat roentgenograms showed that this tumor was increasing in size at a rather rapid rate.

Another patient (case 13) presented an unusual abnormality, which has been described briefly by one of us (A. T. R.).[25] The left labium majus and the entire left lower extremity, except the foot, were diffusely enlarged, being roughly one and a half times as large as the structures on the right. The thickening involved only the subcutaneous tissues, sparing the bone. No nodules could be felt (fig. 2*A*). Many large, circinate, brownish macules covered much of the surface of the skin. In the groin the venules were slightly dilated. There was no pitting of the tissues. The lower limbs were of equal length.

Biopsy of a specimen taken from the left thigh was reported as follows (Dr. C. G. Culbertson): "Sections of the skin and the subcutaneous tissue showed the epidermis to be mildly hyperkeratotic. The dermis appeared moderately thickened, and there was moderate edema of the upper layers of the cutis with mild dilatation of the superficial capillaries and

25. Ross, A. T.: Case of Tuberous Sclerosis, Quart. Bull. Indiana Univ. M. Center **3**:13-15 (Jan.) 1941.

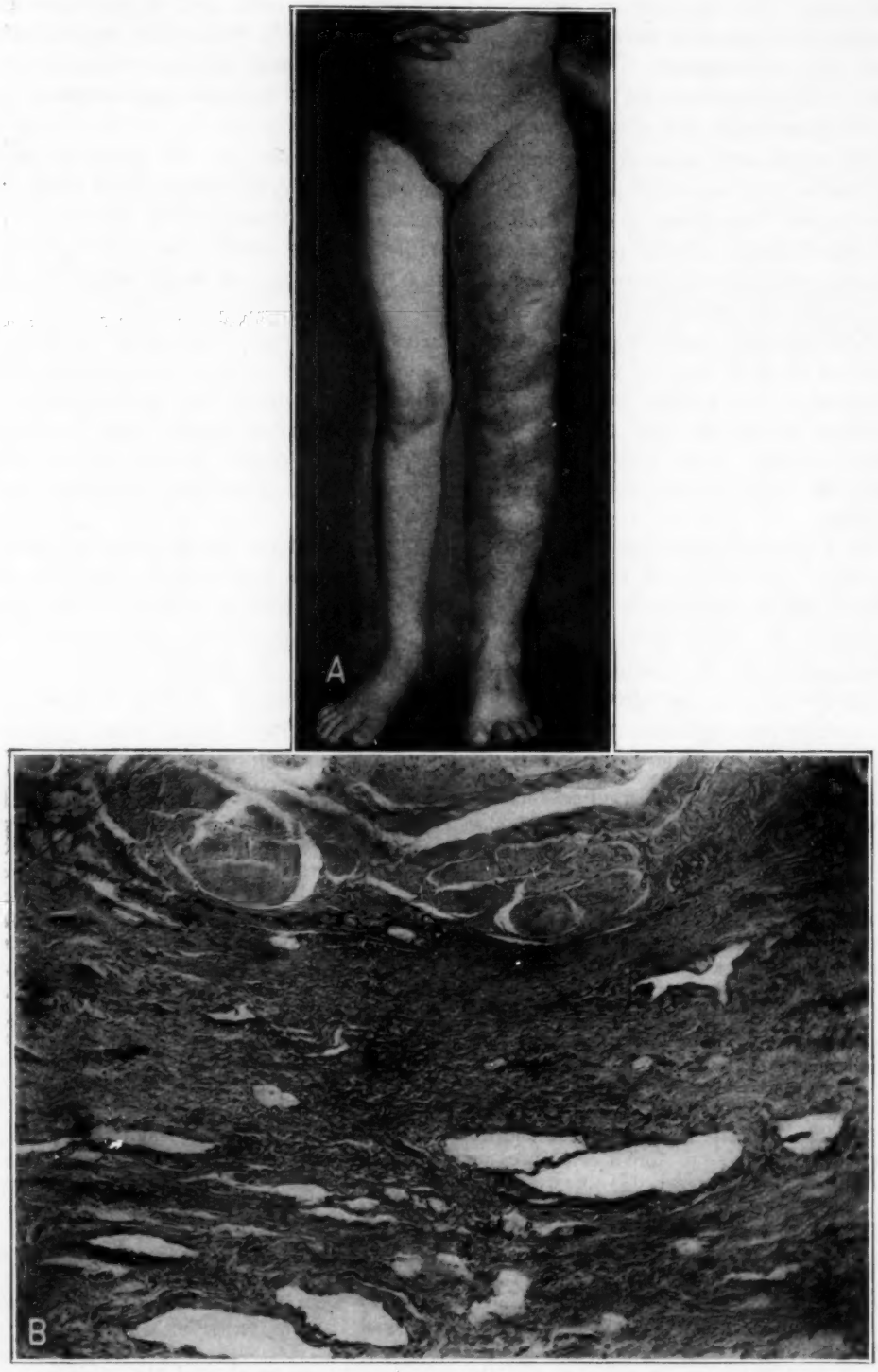

Fig. 2 (case 13).—*A*, hypertrophy of the left labium majus and the left lower extremity. *B*, microscopic section, showing pronounced increase in fibrous tissue, with many dilated blood channels.

perhaps the lymph spaces. There was no pronounced infiltration of inflammatory cells, but in several places about the smaller arterioles a collection of what appeared to be histiocytes surrounded the blood vessels. The endothelium of the capillaries and arterioles showed a decided tendency to proliferate. In these areas, the most notable of which appeared in the papillary layer of the dermis, was a conspicuous deposit of brown pigment, which was shown by ferricyanide stains to be an iron-containing hemoglobin pigment. This pigment was also deposited rather generously about the sweat glands and throughout the deeper layers of the dermis. Beneath the somewhat thickened dermis was a layer of lobulated fatty tissue, and beneath this, an area of dense fibrous tissue, which lay on the skeletal muscle. This deeper layer contained a large number of venous-like, dilated blood channels, which were supported by rather dense collagen connective tissue (fig. 2*B*). Ferricyanide stains showed a great deal of hemoglobin pigment about these blood channels. Examination of slides stained by the trichrome method, as well as with hematoxylin and eosin, failed to reveal any neurofibromatous element.

"Diagnosis: The skin and subcutaneous tissue showed peculiar diffuse angiomatous tissue, with a pronounced tendency to proliferation of the endothelium and perivascular histiocytes."

Dermatologic Lesions.—As mentioned previously, the presence of the characteristic lesions of adenoma sebaceum on the face was the prime factor in the selection of patients for inclusion in this series. Biopsy material was obtained from the facial lesions of 14 patients. The diagnosis was confirmed for 13 of these; for 1 patient the diagnosis was that of chronic inflammation of the skin. Eight patients showed no cutaneous lesions other than adenoma sebaceum.

The brown-pigmented café au lait spots were frequent, occurring in 11 of our patients. In 6 patients these pigmented areas occurred on the back or the flank; in 2, on the forehead; in 1, about the shoulder and axilla, and in 1, on the cheek anterior to the ear. In 1 other patient such a spot involved both lids of the right eye, so that it was difficult for the patient to open the eye.

Firm, fibrotic nodules of the scalp occurred in 3 patients, from 1 of whom a specimen was removed for biopsy. The pathologic diagnosis (Michigan Department of Health) was "tuberous sclerosis, with active degeneration of the hair shafts and small cystic areas forming in the sebaceous glands and extending into the hair shafts, together with outstanding sclerosis and hyalinization of the stroma."

A similar nodule occurred over the sacrum in 1 patient and in the right axilla in 2 others. One patient exhibited a "port wine" nevus over most of the right cheek.

Three patients showed whitened areas of depigmentation on the face, trunk and lower extremities.

One patient had several pedunculated moles on the neck, together with a cyst approximately the size of a hickory nut. The pathologic diagnosis was that of epidermoid cyst. A similar cyst occurred in the left flank of a second patient.

On the left thenar eminence of an 18 year old youth there occurred a solid, flat mass, measuring 3 by 4 by 1 cm., and in the left flank a hard nodule, 3 by 4 cm. Several lymph glands in the left axilla were enlarged and hard. Biopsy showed the mass on the hand to be a squamous cell cancer of grade 2 malignancy.

We did not encounter a single instance of tumor of the nail beds or of deformity and striation of the nails themselves.

Ophthalmoscopic Examination.—Fundoscopic examinations in our series revealed no deviations from normal in 16 patients. One of the patients, a 19 year old girl, once normal, but a helpless idiot at the time of admission, was apparently blind, but there were no retinal changes to account for her loss of vision. Satisfactory visualization of the fundi was impossible in another patient, with hemophilia, who has been mentioned previously. One patient showed only marked increase in retinal pigment; there were no visual changes. Another showed old, inactive chorioretinitis; visual acuity could not be determined.

Six patients had retinal tumors, in 1 of whom the lesion was bilateral. This patient (case 11) has been mentioned previously (*XIV*, fig. 1); his aunt (*VIII*, fig. 1) had a tumor covering the right optic disk. At the time of admission (at the age of 41) visual acuity was 20/20 in her left eye and 10/20 in her right eye. The left disk appeared normal; the right disk had the appearance of early optic nerve atrophy. No tumor was seen in examinations by two observers. Examination one year later showed the presence of a tumor covering all the right optic disk except a narrow segment along the nasal margin. The lesion was yellow and had a coarsely granular appearance. It was roughly oval, measuring 1.5 by 2 disk diameters, with the long axis lying in the 90 degree meridian. There were no vessels over the surface of the mass; several could be seen emerging from beneath its border. Visual acuity was still 10/20. The macula appeared normal. This patient was the oldest in whom such a tumor was observed. The youngest patients with retinal tumor were 4 years 9 months and 5 years of age respectively.

In 4 patients the tumor appeared either to have its origin at the margin of the disk or to cover the major portion of the disk itself. In the 2 remaining patients, 1 of whose cases will be discussed in detail under "Autopsy Material," the involved area was situated above and temporal to the disk.

In appearance none of the tumor masses differed essentially from the description previously given (fig. 3). In none were vessels seen over the surface, and in every instance vessels could be seen to disappear beneath the margins of the lesion. All the tumors were undoubtedly identical with those described by previous authors under the term "phakoma."

Lesions of the Kidney.—In 22 of the 25 patients in this series there was no evidence of a palpable mass in the region of the kidney at the time of the original physical examination. Subsequently, in 1 of these patients palpable tumors developed. Of the 4 patients with palpable masses in the region of the kidney, the involvement was bilateral in 3. In an additional patient bilateral renal tumors were observed at autopsy, the presence of which had not been suspected during his lifetime.

In 3 of the aforementioned patients urinalysis revealed abnormalities. In each instance the findings were characteristic of severe pyelonephritis. The urine of the remaining 22 patients was normal.

It was possible to obtain excretory pyelograms from 17 of the 25 patients. For 8 of these the pyelograms were considered normal. In 4 patients the pelves were enlarged, but the outlines of the kidneys were normal in size, shape and position. In 2 patients the outline of the kidney on the right was approximately twice the normal size; the pelvis appeared normal. In 2 patients the outlines of both kidneys were at least twice the normal size, and the calices were greatly distorted and displaced. In the ninth patient there was a double ureter on the right but no other abnormalities.

Roentgenograms of the Head.—Roentgenograms of the skull were obtained for all 25 patients; for only 5 was the appearance considered normal. For each of the 20 remaining patients, the roentgenograms showed many small, discrete areas of calcification throughout the brain substance. These areas were seen most often in the region of the sella turcica, the basal ganglia and the choroid plexuses. In 2 patients such areas occurred also in the cerebellum; in 2, in the occipital poles, and in 2 others, in the frontal lobes.

Twelve patients presented many round or oval islands of increased density, measuring from 2 or 3 mm. to 1.5 or 2 cm. in diameter. In each instance stereo-

scopic roentgenograms showed these islands to be situated in or immediately beneath the calvarium. On 1 of these patients autopsy was performed; a single flat roentgenogram taken of the calvarium after its removal showed these islands to be in the calvarium; the areas were not present in a roentgenogram of the brain exposed after fixation. In the case of one other patient in whom roentgenograms of the skull revealed similar islands, a roentgenogram of the brain

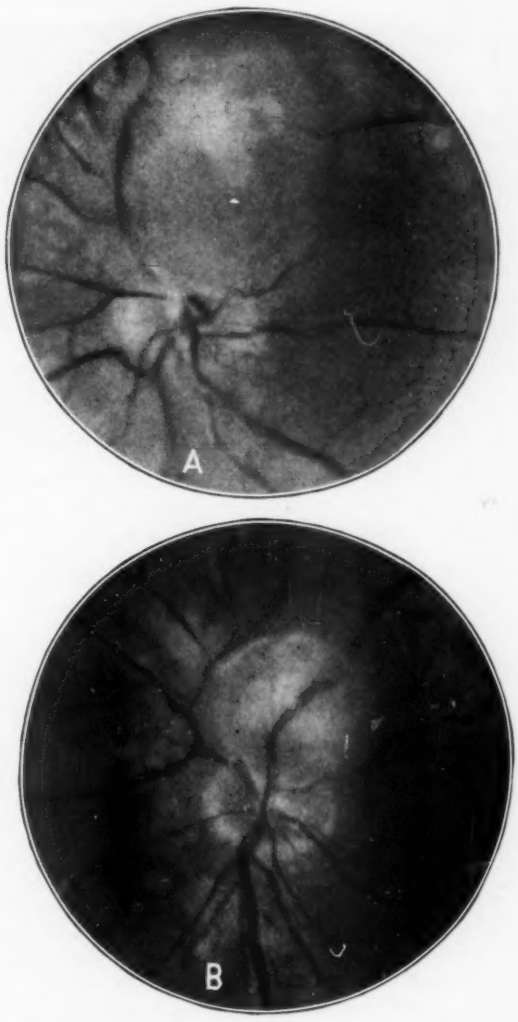

Fig. 3 (case 15).—Appearance of phakomas. *A*, right eye; *B*, left eye.

after fixation failed to show their presence. Unfortunately, a roentgenogram of the calvarium was not obtained.

Pneumoencephalographic Studies.—We obtained encephalograms from 20 of our patients; for another patient we were able to examine encephalograms made elsewhere shortly before his admission here. For only 3 patients were the encephalograms considered normal. In 16 patients there was demonstrated, in addition to the calcifications mentioned previously, generalized atrophy or hypoplasia of the brain. These changes were classified, roughly, as follows: mild, 2 patients; moderate, 9 patients; advanced, 5 patients. In all but 1 of these patients

the dilatation of the ventricular system was symmetric. One patient presented enlargement of one ventricle only, with retraction of the midline structures toward the involved side.

The only lesions pathognomonic of tuberous sclerosis were intraventricular tumors, the so-called candle gutterings. These occurred in 7 of our patients.

Other Roentgenologic Observations.—Flat roentgenograms of the hands were obtained for 18 patients, for 12 of whom the roentgenograms were considered normal. Four had small cysts or areas of rarefaction in the phalanges of some or all of the fingers. Another patient had a solitary cyst in the terminal phalanx of the right index finger, and another, a similar cyst in the head of the first metacarpal bone.

No special study was made to determine the presence of unusual calcification in other parts of the skeletal system. In but 1 instance such changes have been encountered in the occasional roentgenograms taken for other purposes during routine institutional care. In the pyelograms of the patient with the hypertrophy of the left lower extremity mentioned previously, there were observed in the alae of both ilia areas of localized patchy sclerosis, similar to those previously described as occurring in the parietal bones of the skull.

AUTOPSY MATERIAL

Five of the patients, 4 males and 1 female, in this series have died since our study began. The ages at death were 21, 29, 4, 8 and 19 years. The duration of residence in the hospital for these 5 patients was twelve, twenty-three, one-half, one-fourth and four years respectively. Four patients died after a series of seizures. The death of the fifth patient was attributed to renal insufficiency; there were bilateral renal tumors, each the size of a grapefruit, and urinalysis revealed severe pyelonephritis. Permission for autopsy could not be obtained.

Autopsies were performed on 3 patients. Brief clinical abstracts and postmortem observations follow.

CASE 1.—A 19 year old girl had been admitted to the Lapeer (Mich.) State Home and Training School when 7 years old because of mental deficiency and convulsions, which had been present since she was 16 months of age. She was later transferred to the Caro State Hospital for Epileptics. She was able to sit up, but could not stand or walk without assistance and was apparently unable to see. Sebaceous adenomas were present over the face. Over the lower part of the back was a hand-sized, roughened, coarse, tan patch. Similar patches were present on the left shoulder and near the right scapula. The feet were cyanotic and everted; she bore her weight on their medial surfaces. Examination of the chest and abdomen disclosed nothing of significance. The results of the neurologic examination, aside from absence of the abdominal reflexes, were normal.

We present the results of ophthalmic examination in detail because of the lack of reports of similar lesions. We believe that our case is the eleventh to be reported.

Ophthalmic Examination (Dr. Bruce F. Fralick).—Examination of the eyes was rendered difficult by the patient's restiveness. There was bilateral keratoconus. The right fundus appeared normal. In the left eye was a posterior polar cataract. The margin of the disk was blurred. Above and temporal to the disk was a large gray-white area, resembling in some respects glial tissue and in others fluffy exudate. The vessels in this region showed pronounced perivascular infiltration, and the veins were engorged. There was considerable pigmentary disturbance, with many scattered clumps in the upper quadrants of the involved field. The area appeared elevated, with retinal vessels coursing above it. A grayish, nonelevated lesion, with pigmentary and perivascular changes, was present temporal to the macula. Two disk diameters below the disk was a small, flat plaque, which lay beneath the retinal vessels and about which were no pigmentary changes. It was considered that the patient had severe exudative chorioretinitis and probably a phakoma.

Laboratory Data.—A complete blood count, the Kahn test of the blood and examination of the spinal fluid gave normal results. A catheterized specimen of urine gave a 2 plus reaction for albumin and contained a few hyaline casts. A biopsy specimen from one of the facial lesions was diagnosed as "adenoma sebaceum." A specimen taken from the patch of shagreen skin showed thickening of the collagen of the corium with no significant change in the epidermis.

Course in Hospital.—The patient had an average of seven seizures a month during her stay in the institution. About a year after her previous examination a mass about 15 by 8 cm.

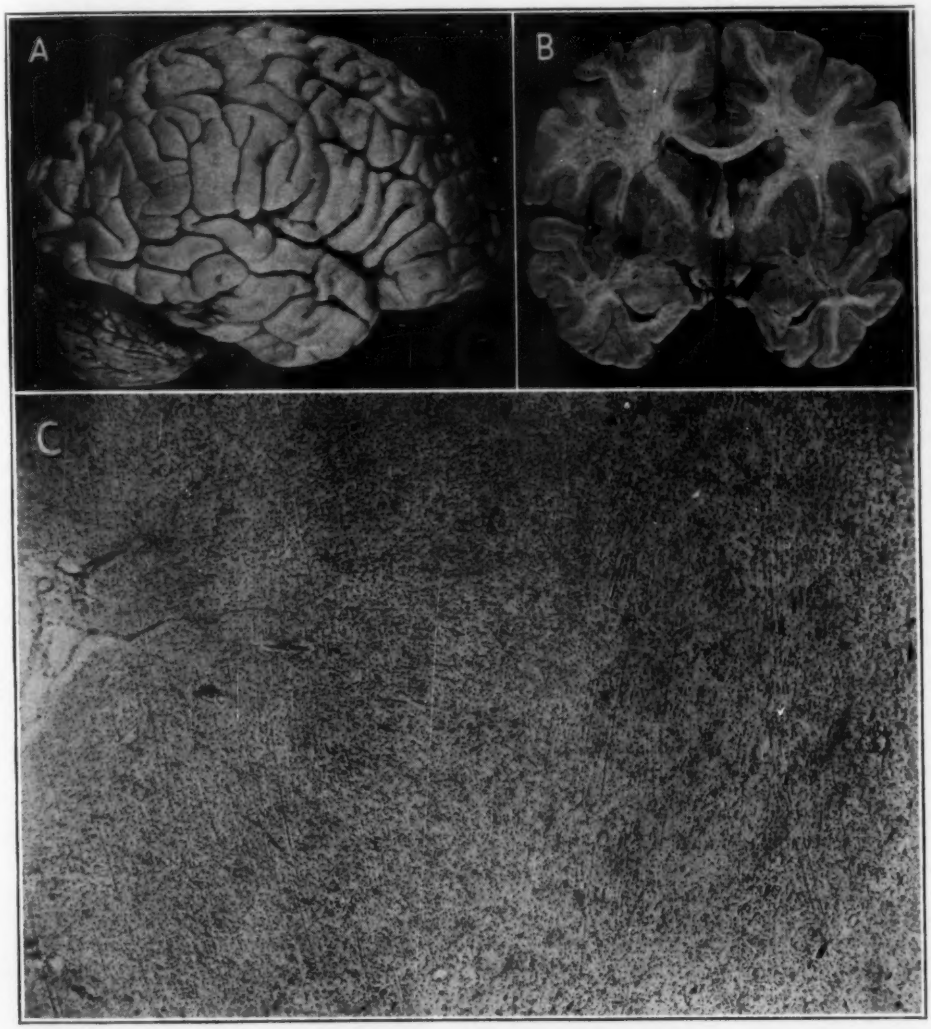

Fig. 4 (case 1).—*A,* external appearance of brain, showing tuberous nodules in the cerebrum. *B,* gross appearance of cortical nodules and subependymal tumors on section. *C,* microscopic appearance of cortical nodules, showing disturbed cytoarchitecture, decrease in nerve cells, proliferation of glia, atypical giant cells and heterotopias in the white matter. Nissl stain.

could be felt in the region of the right kidney and a somewhat smaller one in the area of the left kidney. The patient died in status epilepticus.

General Autopsy Observations.—The lower lobe of the right lung was congested. In the abdominal cavity was a mass extending vertically from the right costal margin to the iliac crest and horizontally from the flank to the midline. The mass was solid, irregular and studded with whitish yellow nodules of varying sizes. A similar, but smaller, mass was in the left hypochondrium. Both tumors were incorporated into, or had replaced, the kidneys (fig. 7 *A*).

Histologic examination of the masses showed countless nodules of various sizes consisting of smooth and striated muscle, connective tissue, fat and occasional proliferations of blood vessels, surrounded by typical renal epithelial tissue. The tumors were designated as myoangiolipofibromatous neoplasms, apparently identical with those reported in the literature in cases of this disease.

Brain.—Gross Inspection: The brain, which was examined at the Neuropsychiatric Institute, Ann Arbor, Mich., weighed 1,100 Gm. The leptomeninges and blood vessels showed no abnormalities. The external configuration of the cerebral convolutions was largely preserved, but their substance was interspersed with numerous white nodules of a hard, cartilaginous consistency. They were present in almost all the main gyri of the convexities, but were fewer on the base and the median surface; about seventeen such nodules could be identified in the left hemisphere and sixteen in the right, but their distribution was not symmetric. The base of the cerebellum was diffusely white, hard and shrunken. On section (fig. 4 *A*), the nodules did not appear sharply circumscribed; they showed a pearly white surface and a grayish discoloration in their depths, with lack of normal demarcation between the gray and the white substance. The lateral ventricles were slightly enlarged but were partially obliterated by numerous grayish white nodules which protruded irregularly into them from the walls, especially in the vicinity of the caudate nuclei (fig. 4 *B*). In the affected regions of the cerebellum the folia were vaguely outlined and partly calcified. The brain stem and the entire spinal cord appeared grossly normal.

Microscopic Examination: Histologically, the cortical nodules presented a profoundly altered cytoarchitecture (fig. 4 *C*). The normal lamination had entirely disappeared, giving place to a disorderly arrangement of neurons, which had greatly decreased in number, and an accumulation of glial elements. The remaining neurons were largely atypical forms, either giant cells with numerous branching processes, or small fusiform neuroblasts. The glial elements varied from slender forms with oval or elongated nuclei and polar processes to scattered atypical, pale, plump, uninucleated or multinucleated giant cells. The giant cell forms occurred either singly or in nests, were widespread in the cortex, including the molecular layer, and were especially numerous in the gyral white matter, their presence accounting for its poor demarcation from the gray matter. The relative proportion of neurons and glial elements varied inversely. In nodules with the greatest paucity of nerve cells there was intense glial proliferation, to almost a neoplastic degree. Such areas in Holzer preparations showed dense transverse bands of gliosis in the superficial and lower layers of the cortex, interconnected by longitudinal columns of fibers. In Weigert preparations the myeloarchitecture had largely disappeared, the heterotopia in the white matter consisting of unmyelinated islets. Secondary changes in the form of degeneration and vacuolation of neurons and microglial reaction were common, but deposition of lipids was nowhere seen. In the intact parts of the cortex the cytoarchitecture was preserved, but there were many primitive types of nerve cells, scattered giant neurons and fewer giant glia cells.

The subependymal nodules were of two types: (*a*) predominantly cellular tumors, consisting of large plump cells, which resembled the giant cells of the cortex, probably astroblasts or plasmatic astrocytes, with few fibers and scattered calcareous deposits, and (*b*) predominantly fibrous tumors, composed of radiating whorls of slender polar elements rich in fibers, which resembled polar spongioblasts and in which calcification was usually pronounced. There was generalized glial proliferation beneath the ependyma.

The corpus striatum contained a preponderance of large neurons, many of which resembled the giant nerve cells of the cortex, and nests of giant glia cells were scattered on their periphery. There were no unusual changes in the thalamus, pallidum, midbrain and pons. In the cerebellum two types of changes were noted: (*a*) nodules in which the cytoarchitecture was disturbed and replaced by radiating whorls of cells resembling polar spongioblasts, with dense gliosis and frequent pronounced calcification, and (*b*) lobular sclerosis of the folia, with characteristic outfall of cells in the Purkinje and granule layers, increase in the Bergmann zone and gliosis of the molecular layer. Heterotopic cells were commonly seen in the cerebellum, medulla and spinal cord, but there were no other specific changes in the cord.

Ophthalmic Study.—The eyes were examined at the Army Medical Museum (accession no. 68196). The report of Col. J. E. Ash follows:

"Gross Examination: Both eyes appeared smaller than normal.

Right eye: The right eye measured 23 by 23 by 22 mm. The cornea was clear and the pupil dilated. The eye was opened in the horizontal plane. The disk appeared slightly elevated and opaque. The vitreous was cloudy and the lens opaque. There was a small area of opaque thickening, measuring 4 by 2 mm., just below the equator.

"Left eye: The left eye measured 23 by 22 by 21 mm. The cornea was clear and the pupil dilated. The eye was opened in the horizontal plane. There were several thickened, opaque areas and two pigmented spots on the fundus.

Fig. 5 (case 1; United States Army Medical Museum, accession no. 69195).—*A*, photomicrographs of a nodule (*1*) and a plaque (*2*) from the right eye. *B*, photomicrograph of plaque from the left eye, showing frayed surface and apparent loss of continuity of the internal limiting membrane. *C*, photomicrograph of plaque from the left eye, showing a calcium-containing hyaline mass involving all layers of the retina. *D*, photomicrograph, showing detailed cellular structure of the plaque from the left eye shown in *B*.

For *A1*, *A2*, *B*, *C* and *D* of figure 5, the negative numbers of the United States Army Medical Museum are 70265, 70264, 70269, 70268 and 70262 respectively.

Microscopic Examination: Right eye: There were two small, circumscribed areas of thickening of the nerve fiber layer, one forming a nodule on the temporal side, the other a plaque posterior to the equator on the nasal side. The ganglion cell layer did not appear to be invaded, although there was some reduction in cells at these points. Beneath the nodular mass the inner nuclear layer was considerably depressed.

"Left eye: Similar, but larger, plaques were present in this eye, one of which had an irregular, frayed surface and had apparently broken through the internal limiting membrane. It also showed some invasion of the ganglion cell layer. At the center of another plaque was a large, lobulated, calcium-containing, hyaline mass which involved all the layers of the retina and was encapsulated by retinal pigment epithelium. Adjacent to the hyaline mass were several smaller colloid excrescences on the lamina vitrea.

"The cells in all the nodules, for the most part, had long fibrillar processes which stained positively for glial fibers with Masson's trichrome stain, phosphomolybdic acid hematoxylin and the Wilder glial stain. There was, however, considerable irregularity in size and shape, the nuclei varying from round to spindle shaped. There was in general a syncytial arrangement. Nucleoli, when present, were usually small, two frequently being apparent. An occasional prominent nucleolus was noted, but this was not the rule. Mitoses were not seen. Blood vessels were present within the nodules, but the vascular supply was not abundant. These nodules were areas of gliosis, but the type of glia cell composing them was not entirely clear; it was probably astrocytic or astroblastic.

"The eyes were otherwise not remarkable, except that on the nasal side of each eye a strand of iris tissue extended forward across the filtration angle to the ligamentum pectinatum. This probably represented imperfect differentiation of the angle of the anterior chamber, rather than a secondary synechia.

"Diagnosis: The diagnosis was multiple, bilateral gliosis of the retina, associated with tuberous sclerosis."

CASE 2.—A woman aged 29, an Austrian Jewess, had a feebleminded grandfather and 2 feebleminded sisters, neither of whom had convulsions or presented facial lesions. Our patient had had a great number of grand and petit mal seizures since the age of 11 years. She had never talked, fed or dressed herself and was untidy. Her mental development was that of an idiot. She was physically underdeveloped and resistive; she usually sat crosslegged and made stereotyped rocking movements. Sebaceous adenomas were present over the face. She walked on everted feet. Both kidneys were palpable, the left seeming to be normal in size and the right slightly enlarged. The external rectus muscles were weak. Far out on the temporal portion of each ocular fundus were some pigment deposits, suggesting old chorioretinitis. On the medial margin of the patch in the right eye was a small, round, yellowish lesion with a nodular appearance. Neurologic examination revealed nothing abnormal.

Laboratory Data.—A complete blood count, a Kahn test of the blood and examination of the spinal fluid gave normal results. The urine contained a trace of albumin and a few granular casts. A biopsy specimen from one of the facial lesions was diagnosed as "adenoma sebaceum."

Course in Hospital.—The patient had seizures recurring at irregular intervals. In the course of a year both kidneys became considerably enlarged, particularly the right. The patient died of bronchopneumonia following serial seizures.

General Autopsy Observations.—Unfortunately, permission to remove the eyes was not obtained. Autopsy disclosed pronounced congestion of both lungs, with consolidation of the lower lobe of the right lung. Both kidneys were considerably enlarged, the right weighing 800 and the left 550 Gm. Their surfaces were firm, irregular, nodular and pinkish yellow. Neither adrenal gland appeared involved in the mass (fig. 8 *B*).

Histologic examination of the tumor nodules revealed them to be rhabdomyomas undergoing extensive fatty degeneration. The adrenals appeared normal.

Nervous System.—Gross Inspection: The brain and spinal cord weighed 1,050 Gm. The macroscopic observations resembled essentially those in case 1, viz.: numerous nodules in both cerebral hemispheres; nodular, atrophic folia at the base of the cerebellum, and subependymal tumors in the ventricles, including the third ventricle.

Microscopically, the lesions in this case differed somewhat from those in the previous case. In the cortical nodules, although a similar disturbance of the cytoarchitecture, with atypical giant neurons and glia cells, was observed, gliosis was less advanced. These nodules merged imperceptibly with the "intact" cortex, which had a poorly defined cytoarchitecture and contained neuroblasts and giant cells. Heterotopias occurred not only near the cortex but deep in the white matter; these areas appeared in the Weigert preparations as disseminated, unmyelinated islets, in Holzer preparations as foci of gliosis and with the Nissl stain as collections of giant cells, as well as of relatively "normal" neurons. Glial rosettes were also

common. The subependymal tumors were either predominantly cellular or predominantly fibrous, but on the whole showed a more rapid growth. Such signs as increased vascularity, necrosis, hemorrhages and mitotic figures were prominent, while calcification was less pronounced. Of special interest was the presence of such a tumor in the occipital cortex. In the cornu ammonis there was characteristic sclerosis of Sommer's sector. The changes in the corpus striatum and the cerebellum were similar to those in case 1. It was noteworthy that the changes in the cerebellar nodules (fig. 6) extended beyond them into the white matter of the adjacent folia. The brain stem and the spinal cord showed only scattered heterotopic and atypical cells.

CASE 3.—An idiot boy aged 4 years, of excellent family background, had had sudden, momentary attacks of bobbing of the head, rolling of the eyes, twitching of the muscles and loss of consciousness. He had never walked or talked and showed little interest in his surroundings. A rash on the face had been present since his second year. When he was 1 year old, encephalograms taken at Henry Ford Hospital, Detroit, demonstrated pronounced dilatation of the lateral and third ventricles. By means of a trephine opening, made a month later, the presence of free communication between the ventricular and the subarachnoid system was proved. He was overnourished, with flabby musculature; he could sit but not stand alone. Sebaceous adenomas were present on the face; in addition, there was a brownish, corrugated patch of skin, 1 by 2 cm., on the right temple. The ocular fundi were normal. The kidneys were not palpably enlarged. Neurologic examination revealed nothing abnormal.

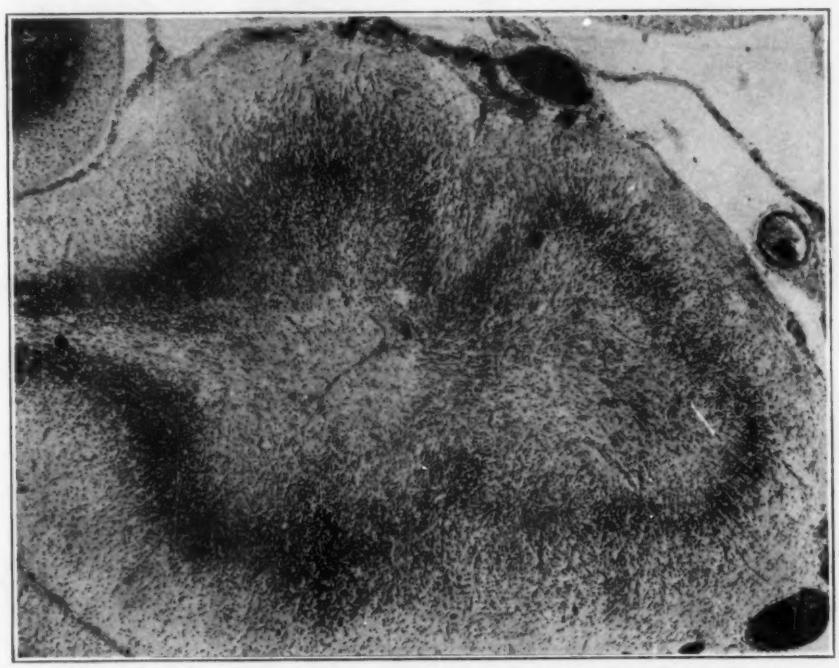

Fig. 6 (case 2).—Photomicrograph of cerebellar nodule, showing involvement of the white matter of adjacent folia.

Laboratory Data.—A complete blood count, urinalysis, a Kahn test of the blood and examination of the spinal fluid gave normal results. The patient died after serial seizures.

Autopsy.—There was considerable pulmonary edema. The left kidney had several subserous cysts, which, when opened, released a small amount of clear fluid. On the upper pole was a hard mass, 2 cm. in diameter, which on section expanded slightly and was pale yellow. A number of small subserous cysts, as well as a 2 mm. tumor, were present on the surface of the right kidney (fig. 8).

Histologic examination of the renal lesions showed many small tumors of rather complex structure. They were considered to be rhabdomyomas.

Nervous System.—The brain weighed 1,475 Gm. and showed macroscopically the characteristic cortical nodules and subependymal tumors. The entire inferior surface of the cerebellum

was white, shrunken and hard. There was a peculiar enlargement of the cisterna magna, causing a deep concavity between the brain stem and the cerebellum, the latter appearing to be reduced in size (fig. 7 *A*). Probably associated with this anomaly was extensive internal hydrocephalus, resulting in thinning out of the corpus callosum, the fornix and the septum pellucidum (fig. 7 *B*).

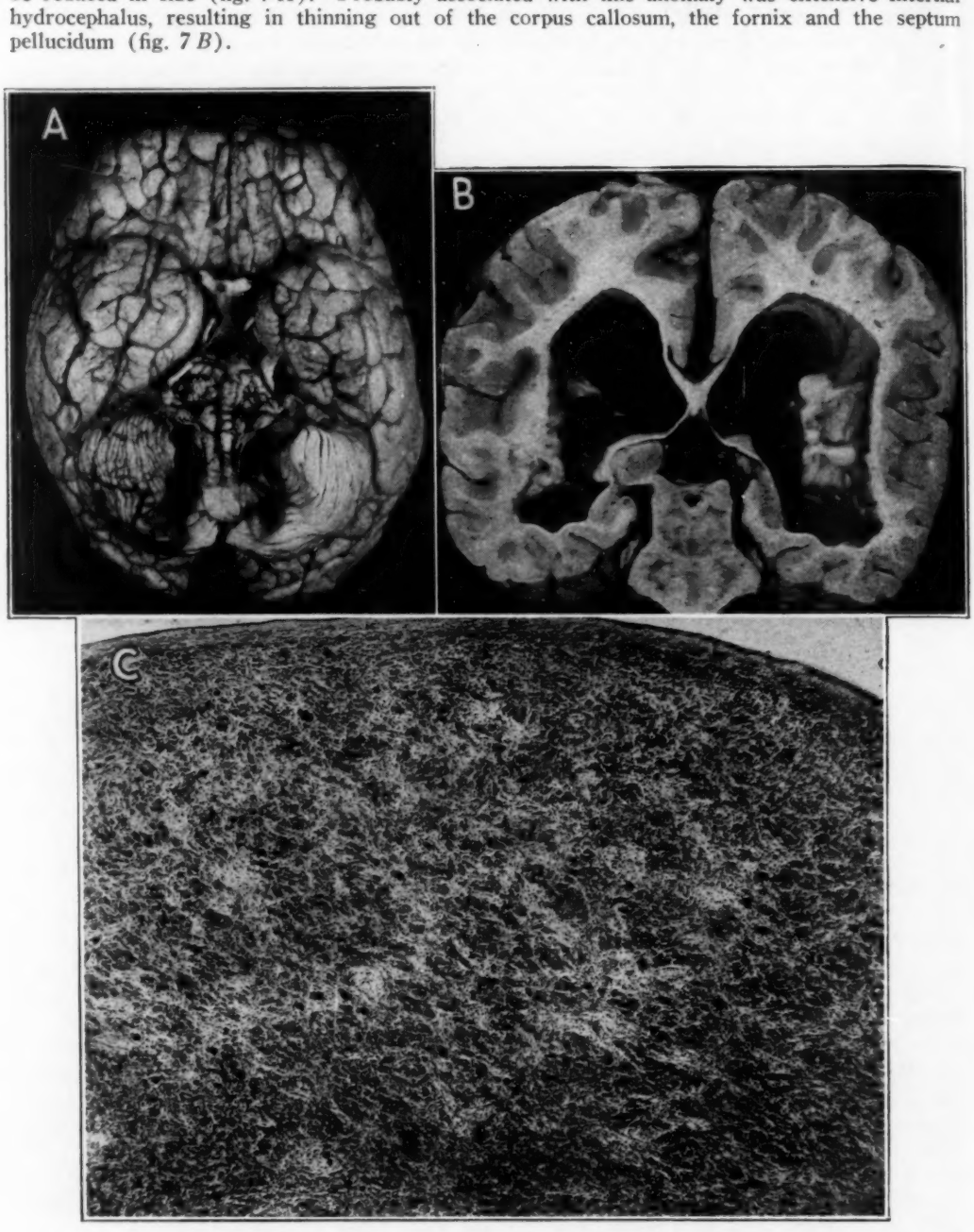

Fig. 7 (case 3).—*A*, base of the brain, showing anomaly of the cisterna magna and white shrunken appearance of the inferior surface of the cerebellum. *B*, gross section, showing hydrocephalus and intraventricular tumors. *C*, microscopic appearance of subependymal tumor, which is primarily cellular and which contains scattered calcareous deposits. Nissl stain.

Microscopically, the changes closely resembled those in case 1. There were only minor differences, such as less advanced glial proliferation in the cortical nodules, and the heterotopias in the white matter were composed predominantly of nests of giant glial cells rather than of

neurons. The subependymal tumors were, again, either predominantly cellular (fig. 7 *C*) or predominantly fibrous, calcification being prominent and necrosis minimal. The changes in the corpus striatum were similar to those in the preceding cases. An unusual feature was the presence of extensive gliosis and atypical glia cells in the optic tracts. No typical nodules or calcifications were seen in the cerebellum, the changes being entirely those of lobular sclerosis of all folia in the inferior parts of the hemispheres and the vermis, with gliosis of the white matter and the dentate nucleus. There were misplaced Purkinje cells in the various layers and meninges and foci of giant glia cells deep in the white matter. The brain stem

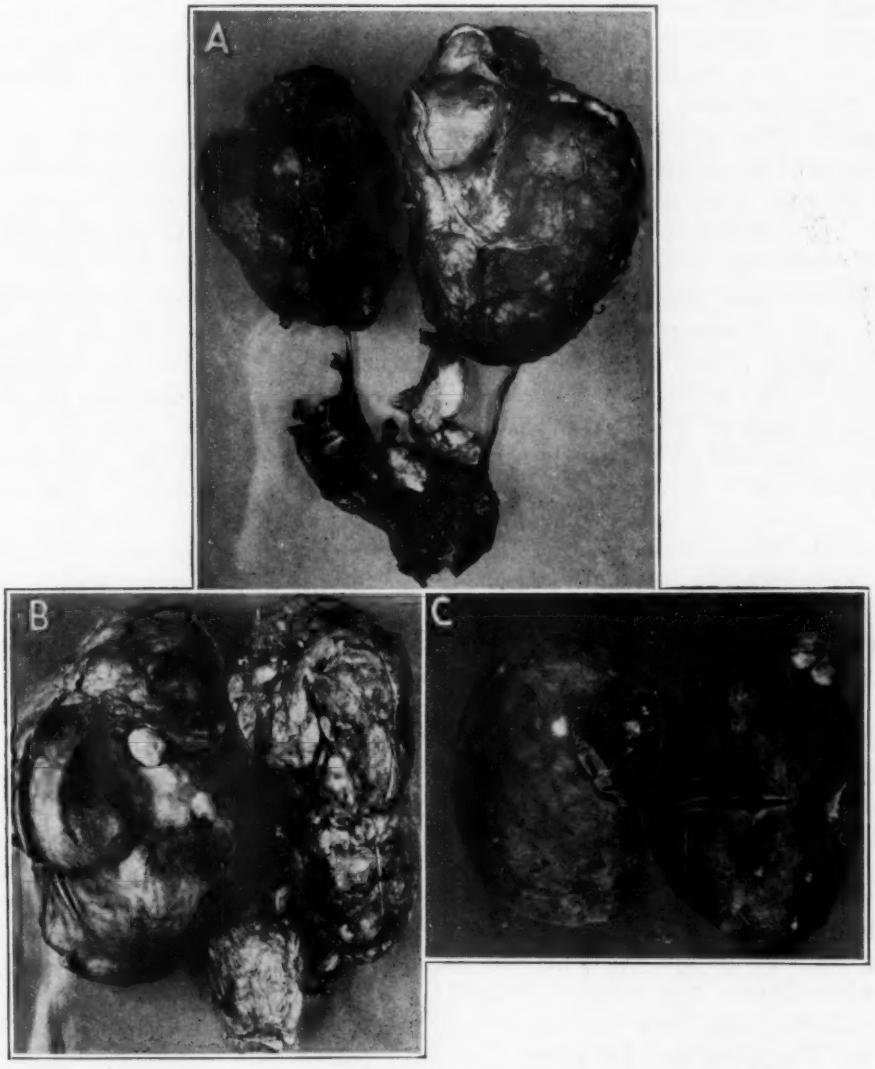

Fig. 8.—*A* (case 1), gross appearance of renal tumors, ureters and bladder. *B* (case 2), gross appearance of renal tumors, ureters and bladder. *C* (case 3), kidneys, showing numerous subserous cysts with nodular tumor at the upper pole of the right kidney.

was not involved. The spinal cord showed diffuse glial proliferation in the posterior columns, scattered heterotopic neurons but no other specific changes.

COMMENT

It is our opinion that tuberous sclerosis is not as infrequent in this country as was formerly believed and that there is no notable difference in its incidence here and abroad. The report of Butterworth and Wilson Jr.[12] and this study indicate

approximately the same frequency here as in England. As mentioned previously, its incidence among patients newly admitted to the Caro State Hospital for Epileptics is 0.56 per cent. At the time of writing there are 17 living patients in a resident population of 1,408 patients at the Caro State Hospital, an incidence of 1.2 per cent. Anderson [26] estimated the general incidence of epilepsy in Michigan to be 210 per hundred thousand, or 0.2 per cent. On this basis the occurrence of tuberous sclerosis in the general population would be 2 per hundred thousand, or 0.002 per cent. It is quite likely that the actual incidence is somewhat less than this figure, inasmuch as most patients with this disease require custodial care and tend to gravitate toward institutions devoted to the care of the epileptic and the feebleminded.

Neither does it seem likely that the predominance of the female sex is as great as was previously indicated in reports of small series of cases. There is no doubt that more females than males present this syndrome, but a review of these reports indicates that the disparity between the sexes is far less than was formerly believed.

Although most patients with tuberous sclerosis present the usual triad of idiocy, epilepsy and adenoma sebaceum, a review of the literature indicates that there may be many variations in the clinical picture. It is theoretically possible for the facial lesions to be present without cerebral involvement, although no clearcut instance of such an occurrence has been described. Critchley and Earl [14] stated that it is likely that such cases do occur, with slight changes in the cerebral cortex, which differ only in degree from those associated with epiloia. Case reports indicate that cerebral lesions may be present without cutaneous or visceral lesions and without convulsions and that epilepsy alone may be the only indication of cerebral involvement. Because nearly all the patients in this series were observed in a state hospital for epileptic persons, it has not been possible for us to study a patient in whom the cerebral lesions of tuberous sclerosis were present without concomitant convulsions. Neither have we observed at autopsy cerebral lesions in the absence of the characteristic dermatologic lesions.

We were able to obtain information regarding the age at the appearance of the facial lesions for only half our patients. The lack of data in this respect is apparently due to failure on the part both of the parents and of the general practitioner to realize the significance of such lesions. The information regarding the appearance of other dermatologic lesions is so scant as to be of no value. It is not recorded that the diagnosis of tuberous sclerosis was made in any case before admission. It is evident that the facial lesions practically always preceded the convulsions. Two of our patients did not present sebaceous adenomas until after their admission to the hospital. One of the patients had had convulsions for four years and the other for twelve years. For both the diagnosis of adenoma sebaceum was confirmed by biopsy. In most patients the convulsive phenomena occurred early in life. In 68 per cent the onset of convulsions occurred before the age of 1 year; in an additional 16 per cent seizures developed between the ages of 1 and 5 years. The correlation between the age of onset of convulsions and the intelligence quotient is so close to that for all types of convulsive disorders as to be entirely lacking in significance.

We have little to add to the comments of other authors regarding the surprising paucity of physical and neurologic changes in persons with such extensive lesions of the visceral and central nervous systems. Our report on concomitant lesions

26. Anderson, C. L.: Epilepsy in State of Michigan, Ment. Hyg. **20**:441-462 (July) 1936.

not described elsewhere (cases 13 and 21) is only evidence that no part of the human system is exempt from involvement in the generalized process.

Although we cannot confirm the statement of Hyman [10] that renal tumors occur in 80 per cent of cases of tuberous sclerosis, there is no doubt that the incidence of such lesions is high. They were present in all 3 patients on whom autopsy was done. Two other patients had palpable masses in the region of the kidney. In 47 per cent of the patients subjected to excretory pyelography there was evidence of abnormality, the exact nature of which could not be determined by the methods of examination available to us. The neoplasms observed at autopsy were essentially similar to those described by other authors as occurring in cases of tuberous sclerosis. They apparently developed from embryonal cell rests. The lesions occurring in the 4 year old boy undoubtedly represented an early stage of those which reached such large proportions in the other 4 patients. These tumors consisted of a conglomerate proliferation of various mesothelial elements—striped muscle, fat, fibrous tissue and blood vessel components. When such tumors degenerate or become malignant, they apparently expand rapidly. Curiously, examinations of the urine did not reflect the profound extent of the changes in the kidney.

Our observations on the roentgenograms of the skull were not essentially different from those reported elsewhere. We consider that two changes were of special diagnostic significance. The first, and most characteristic, was that of patchy zones of increased density, usually situated in the upper half of each parietal bone. These zones were observed in 48 per cent of our patients. Yakovlev and Corwin [17] described them as "brain stones," although other authors have reported them as being located in the calvarium. We have demonstrated that they were actually in the skull. Hall [18] suggested that such lesions are seen only in patients with evidence of neurofibromatosis, as well as of tuberous sclerosis, and that they are of neurofibromatous origin. We have not been able to agree with this suggestion. The second change was that of partially calcified nodular lesions in the region of the basal ganglia or about the third ventricle, and occasionally in other parts of the brain. These nodules occurred in 80 per cent of our patients. As was mentioned previously, they may be confused with calcifications in the glomus of the choroid plexuses and in the pineal body.

The presence of intraventricular tumors, when demonstrated in the pneumoencephalogram, is pathognomonic. Such tumors occurred in 35 per cent of the patients subjected to this form of examination.

Thirty-three per cent of the patients subjected to roentgenographic examination of the hands showed circumscribed areas of rarefaction in some or all of the phalanges. The terminal phalanges were the usual sites. Lesions similar to these are also associated with Boeck's sarcoid and with leukemia, as well as with Recklinghausen's disease and hence cannot be considered pathognomonic of any of the various manifestations of the neurocutaneous syndrome.

Intraocular tumors occurred in 6 patients. Because only a few of these tumors have been studied pathologically, it is not yet possible to classify them with certainty. However, it is generally held that the tumor derives from cells of the glial series. Van der Hoeve expressed the opinion that the tumor cells are neurocytes which have not yet differentiated into either glia or ganglion cells and that they are descendants of the first anlage of the retina. Miss Ida Mann examined a patient's eye submitted to her by Messinger and Clarke [27] and expressed the

27. Messinger, H. C., and Clarke, B. E.: Retinal Tumors in Tuberous Sclerosis, Arch. Ophth. **18**:1 (July) 1937.

opinion that the tumor arose in stage 2 of retinal differentiation (the sixth to the twelfth fetal week) from glia cells of the inner neuroblastic layer. Grinker [28] stated that histologically the characteristic cell is the same as that noted in the nodules in the brain. He assumed that this retinal tumor is probably an astroblastic neoplasm with low growth possibilities. Tarlau and McGrath [29] agreed with Grinker. In our case the retinal nodules were areas of gliosis composed of cells of a type not entirely clear, but probably astrocytic or astroblastic. This adds further support to the glial origin of the tumor. In general, the histologic descriptions given by the authors just mentioned are similar to the observations in our case. Apparently, the cellular structure of the retinal tumor associated with tuberous sclerosis differs from that in Recklinghausen's disease, for in a case of intraocular neuroma reported by Stallard [30] the nodule was made up of irregular clumps and sweeping bundles of neurocytes and neurofibers.

Whether one regards this disease entity as primarily neoplastic or as agenetic, it is to be expected that evaluation of the various etiologic factors usually considered in any study of epilepsy would not reveal anything of unusual significance which would serve to differentiate tuberous sclerosis from any other convulsive disorder. If, as we believe, the so-called etiologic factors represent trigger mechanisms which release the convulsive discharge in a person predisposed to convulsions, then the presence of tuberous nodules in the cerebrum should be regarded in the same light as any other neoplasm or malformation in the precipitation of such a disorder. Except in the family presented in figure 1, the hereditary factors are certainly no more outstanding than those in any similar number of institutional epileptic patients without tuberous sclerosis. The family presented, while unusual, is equaled by many others in our institution records in the number of tainted members it contains.

We have not been able in our series of patients to demonstrate unequivocally a relation between tuberous sclerosis, neurofibromatosis, encephalotrigeminal angiomatosis and rheostosis. However, the evidence presented by the family chart in figure 1 strengthens considerably the assumption that these conditions are closely allied. Also, a number of the other patients exhibited on the face, scalp and trunk lesions which resembled those seen in Recklinghausen's disease, and it is perhaps proper to assume that such lesions offer prima facie evidence of a genetic relationship. From reports in the literature, further support can be adduced that these four dysplastic disorders are allied. The fibrocystic changes, hyperostoses and cysts of the bones of the extremities are seen in all four conditions. The peculiar mottling noted in roentgenograms of the skull, while found more frequently in cases of tuberous sclerosis, has been described also by Lehman [31] in a case of neurofibromatosis, by Dalsgaard-Nielsen [32] in a case of neurofibromatosis and tuberous sclerosis and by Hall in a case presenting characteristics of neurofibromatosis and tuberous sclerosis. More convincing evidence of an allied histogenesis is the observation by Globus [21] of a neurofibroma of the mamillothalamic tract in a patient with abortive tuberous sclerosis.

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28. Grinker, R. R.: Tumors of the Retina, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1058.

29. Tarlau, M., and McGrath, H.: Pathological Changes in the Fundus Oculi in Tuberous Sclerosis, J. Nerv. & Ment. Dis. **92**:22 (July) 1940.

30. Stallard, H. B.: A Case of Intra-Ocular Neuroma (von Recklinghausen's Disease) of the Left Optic Nerve Head, Brit. J. Ophth. **22**:11 (Jan.) 1938.

31. Lehman, E. P.: Recklinghausen's Neurofibromatosis and the Skeleton, Arch. Dermat. & Syph. **14**:178 (Aug.) 1926.

32. Dalsgaard-Nielsen, cited by Hall.[18]

It seems that the close relation between the various manifestations of the neurocutaneous syndrome is best explained on the basis that all three disorders are developmental tissue dysplasias. Patients with tuberous sclerosis frequently exhibit, besides ectodermal dysplasias, developmental anomalies of mesodermal elements as well, an association of defects which binds this disease with a number of other conditions having as their common denominator a disorganization in embryogenesis, whatever the unbalancing factor may be. Since the retinal tumors in tuberous sclerosis seem to derive from the glial elements during the second stage of retinal differentiation, and since the spongioblasts of the neural tube begin to differentiate at about the same period of fetal development, additional weight is given to the theory that this disease is essentially a disorder of development rather than a primary neoplasia. Another factor to be considered is the frequent history of early onset of convulsions. This early appearance is characteristic of all types of cerebral agenesis in which convulsions appear, but especially of the cytoarchitectural type of malformation.

SUMMARY

We present a study of a series of 25 patients with tuberous sclerosis in which the frequency of many of the conditions associated with this syndrome is further established. Two additional anomalies not previously reported are described. A detailed description of the pathologic features of the retinal tumors present in 1 patient is added. The chief diagnostic roentgenographic change, that of patchy zones of increased density in the skull, is conclusively shown to be located in the calvarium. Further evidence is adduced that tuberous sclerosis is a developmental tissue dysplasia.

Dr. V. C. Johnson, department of roentgenology, University Hospital, Ann Arbor, Mich., reviewed all the roentgenographic material, and Dr. Nathan Malamud, of the Neuropsychiatric Institute, Ann Arbor, Mich., examined the brains and spinal cords submitted from autopsy material and furnished many of the illustrations.

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HISTOLOGIC STUDIES OF THE BRAIN FOLLOWING HEAD TRAUMA

III. POST-TRAUMATIC INFARCTION OF CEREBRAL ARTERIES, WITH CONSIDERATION OF THE ASSOCIATED CLINICAL PICTURE

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AND
I. MARK SCHEINKER, M.D.
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For the surgeon faced with the practical problem of treating injuries of the head there remain at least two great unsolved problems. These are the vascular alterations related to edema and hemorrhage within the brain substance and the disturbances in circulation of the cerebrospinal fluid. From the field of intracranial tumor surgery have come most of the significant contributions to the present, somewhat inadequate, understanding of the latter problem. The most recent additions to knowledge have concerned herniation of the uncus of the temporal lobe through the incisural notch. The subject has been elaborated on in a series of papers, among which may be cited those of Meyer,[1] van Gehuchten,[2] Jefferson,[3] Reid and Cone,[4] Moore and Stern,[5] Smyth and Henderson[6] and Schwarz and Rosner.[7] Some of these authors have noted the same phenomenon in association with epidural and subdural hematomas. Thus, it now has been amply demonstrated that space-consuming lesions may cause appreciable herniation through the tentorial opening. Furthermore, in the presence of unilateral lesions there may occur a significant shift of the third ventricle and the aqueduct of Sylvius and obliteration of the cisternae ambientes, with profound disturbance in cerebrospinal fluid flow. Associated changes in neural structures cause striking dysfunction, ranging from pupillary alterations to decerebrate rigidity and death.

These same studies have shown that profound vascular alterations affecting the occipital lobe and the brain stem occur in some cases of neoplasm. Thus, Moore and Stern described infarction of the occipital lobe and attributed it to compression of the posterior cerebral artery by the herniating uncal pole, displaced by tumor tissue. The alterations in the brain stem are the result, they suggested, of sudden changes in the relationship of pressures above and below the

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the Department of Surgery, University of Cincinnati College of Medicine.

1. Meyer, A.: Herniation of the Brain, Arch. Neurol. & Psychiat. **4**:387 (Oct.) 1920.

2. van Gehuchten, P.: Le mécanisme de la mort dans certains cas de tumeur cérébrale, Encéphale **2**:113, 1937.

3. Jefferson, G.: The Tentorial Pressure Cone, Arch. Neurol. & Psychiat. **40**:857 (Nov.) 1938.

4. Reid, W. L., and Cone, W. V.: Mechanism of Fixed Dilatation of the Pupil Resulting from Ipsilateral Cerebral Compression, J. A. M. A. **112**:2030 (May 20) 1939.

5. Moore, M. T., and Stern, K.: Vascular Lesions in the Brain Stem and Occipital Lobe Occurring in Association with Brain Tumors, Brain **61**:70, 1938.

6. Smyth, G. E., and Henderson, W. R.: Observations on the Cerebrospinal Fluid Pressure on Simultaneous Ventricular and Lumbar Punctures, J. Neurol. & Psychiat. **1**:226, 1938.

7. Schwarz, G. A., and Rosner, A. A.: Displacement and Herniation of the Hippocampal Gyrus Through the Incisura Tentorii, Arch. Neurol. & Psychiat. **46**:297 (Aug.) 1941.

tentorium, changes which predispose to arterial congestion and hemorrhage in the rostral end of the brain stem.

From these many studies several significant points emerge:

1. Herniation of the temporal lobe may occur in association with tumor or with meningeal hemorrhage (epidural or subdural).

2. Such a herniation may interfere seriously with cerebrospinal fluid dynamics and be a serious threat to life (Smyth and Henderson).

3. There may occur in an occipital lobe changes which have generally been interpreted as ischemic in origin, resulting directly from compression of the posterior cerebral artery by the uncal herniation (Moore and Stern), or indirectly, from compression of the stretched artery over the displaced third nerve (Reid and Cone).

4. Hemorrhages may develop in the upper part of the brain stem, producing dysfunction, which may rapidly advance to the stage of decerebration.

It is the purpose of the present contribution, one in a series dealing with the results of trauma to the head, to draw attention to several significant observations:

1. The shift of the temporal lobe and the associated uncal herniation are not the result solely of the space-consuming action of the meningeal hemorrhage, but may be caused by the increasing volume of the subjacent traumatized cerebral tissue.

2. To the compressive effect of the edema of the temporal lobe must be added that of the edema of the occipital lobe resulting from the vascular disturbances therein that have been ascribed to infarction of the posterior cerebral artery.

3. Actually, infarction of the posterior cerebral artery is not in itself a completely satisfactory explanation of the changes observed in the occipital lobe.

4. The vascular alterations observed in the brain are not limited to the distribution of the posterior cerebral artery, and indeed may be minimal in the distribution of that artery but maximal in the course of the anterior or the middle cerebral artery.

5. Another, and perhaps more satisfactory, explanation may be advanced for the changes in the brain stem.

6. Significant structural changes in the brain stem short of hemorrhage may occur, and, from the standpoint of prevention of more severe damage, early recognition of the existence of such changes is imperative.

PRESENTATION OF CASES

CASE 1.—*Slight injury to the head in May 1938, followed by headache of gradually increasing severity. Onset of coma Aug. 24, 1938. Lumbar puncture, with withdrawal of excessive fluid, followed by accentuation of signs; exploratory burr holes; evacuation of subdural hematoma. Death. Autopsy: Infarction of occipital lobe and hemorrhage in brain stem.*

History and Course.—W. R., aged 56, sustained a slight laceration of the scalp when he was struck on the head by the hook of a traveling crane in May 1938. Subsequently, headache of increasing intensity developed. On the morning of Aug. 24, 1938 he was admitted to the hospital, at which time the results of neurologic examination were reported to be negative. That afternoon, however, he became comatose. Examination then showed small, fixed pupils and rigidity of the extremities, which was more pronounced on the right side. Lumbar puncture revealed an initial pressure of 260 mm. of water. An excessive amount of fluid (10 cc.) was removed; in addition, jugular compression was done. There were 10 cells per cubic millimeter of spinal fluid.

His coma deepened in the late afternoon. A neurologic consultant was called, and a diagnosis of unlocalizable cerebral neoplasm or subdural hematoma was made. Occipital burr openings were placed bilaterally that evening. The right side of the brain appeared normal. On the left side a subdural hematoma was encountered, and about 50 cc. of a reddish brown fluid was released under considerable pressure. Consciousness was never regained, however, and the patient died the next morning.

Gross Anatomic Observations.—A large subdural hematoma with a well defined capsule was noted overlying the left hemisphere. The appearance of the intact brain is shown in figure 1 and that of the coronal sections in figure 2. Several points should be noted in figure 1: the hemorrhagic infarction in the left occipital lobe and the fulness of this lobe as compared with the right; the fulness of the left temporal lobe and the uncal herniation, and the shift of the midbrain to the right. Striking, also, are the hemorrhages present in the crossing fibers of the pons, as well as in the tegmen. Figure 2 illustrates, again, the fulness of the left temporal and occipital lobes, and the compression taking place at the fissure between the left uncus and the brain stem may be clearly seen in the middle of the three large blocks.

Microscopic Observations.—Sections were taken from the left occipital lobe and from the left third nerve. The sections of the occipital lobe showed perivascular hemorrhages of petechial character scattered in clusters throughout the various layers of the cortical ribbon (fig. 3). Most of the cortical vessels were maximally distended. In some areas the blood vessels were cuffed with polymorphonuclear leukocytes and surrounded by large areas of

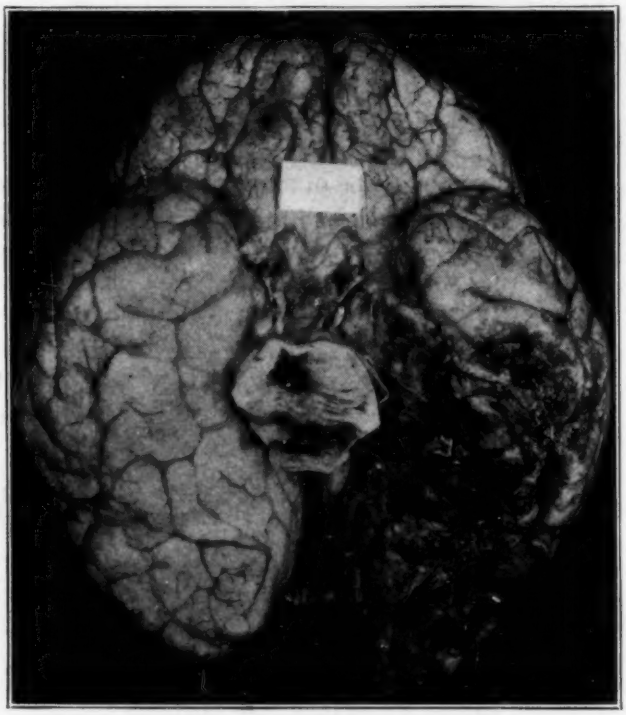

Fig. 1 (case 1).—Left subdural hematoma. Note herniation of the left uncus, infarction in the left occipital lobe, shift of the midbrain and hemorrhage in the midbrain.

necrosis (fig. 4). In these zones the nerve cells showed typical ischemic changes: pale-staining cytoplasm, loss of Nissl granules and deeply staining nuclei. The glia of the cortical ribbon was little altered, though occasional early evidence of clasmatodendrosis was seen. Gitter cells were absent.

In the white matter was relatively little hemorrhage. There were, however, signs of stasis and prestasis. The perivascular spaces were distended with serous fluid, and there was an alveolar, sievelike appearance of the white matter.

Sections taken from the left third nerve at the site of its kinking about the posterior cerebral artery showed hemorrhage on one side of the kinking and none on the other, evidence of the severity of pull on the nerve and, in turn, on the posterior cerebral artery (fig. 5).

CASE 2.—*Severe injury to the head. Coma twenty-four hours later. Exploratory burr openings in temporal region, showing thin subdural hematoma on left side. Death forty-four hours after operation. Autopsy: large subdural hematoma lying under left temporal lobe; edema of left hemisphere, herniation of left uncus and infarction of left occipital lobe.*

History and Course.—M. V., a man aged 70, had fallen forward, striking his face. He was admitted to the hospital on the following day because of the development of coma about twenty-four hours after the accident. Examination showed, in addition to deep coma, equality of the pupils, which were 2.5 mm. in diameter and reacted to light through a small range. The right extremities were flaccid; the plantar responses were of extensor type; the initial pressure on lumbar puncture was 125 mm. of water, and the fluid was grossly bloody.

Operation was carried out two hours after admission, a burr hole being placed in each subtemporal region. These openings were not enlarged, despite the presence of a thin sub-

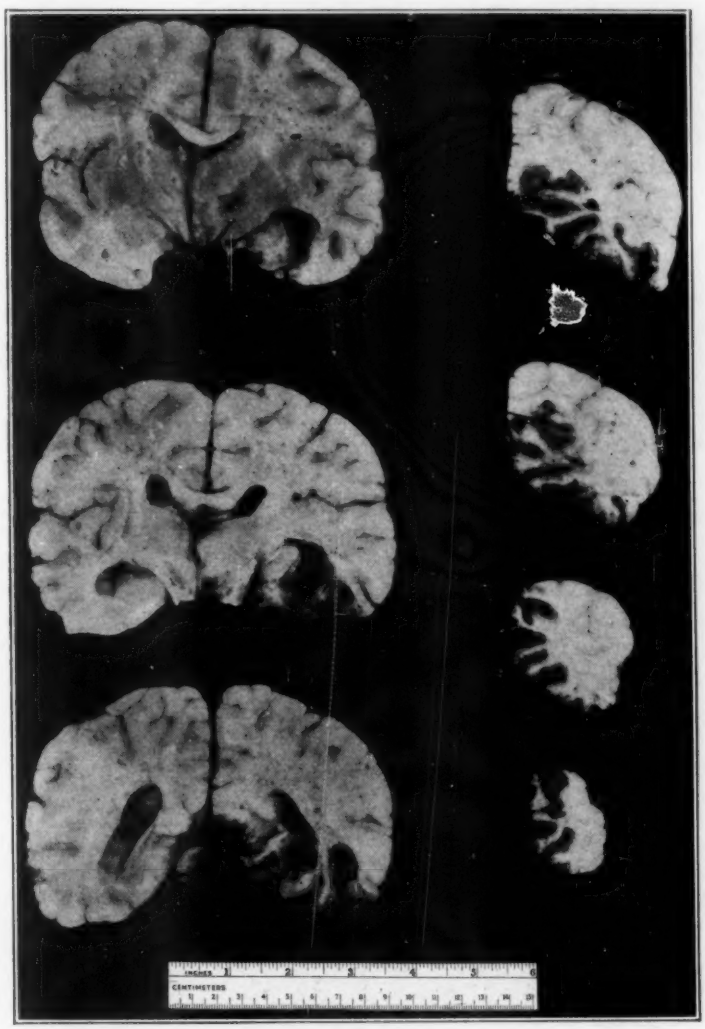

Fig. 2 (case 1).—Infarction in the occipital lobe, fulness of the occipital and temporal lobes, shift of the hind end of the third ventricle and obliteration of the fissure between the left uncus and the midbrain.

dural clot on the left side. On the succeeding day, twenty-six hours after operation, lumbar puncture showed an initial pressure of 300 mm. of water. Death occurred forty-four hours after operation.

Gross Anatomic Observations.—Autopsy, performed seven hours after death, showed terminal acute bronchitis and confluent lobular pneumonia, myocardial degeneration and fibrosis and moderately advanced generalized arteriosclerosis.

The gross changes in the brain are well shown in the photographs (figs. 6 and 7). Attention may be directed to the fulness of the left uncus and to the shifting of the pons to

the right, the shifting of the ventricular system due to the edema of the left hemisphere, as shown in the coronal sections, and the infarction, of relatively limited distribution, in the course of the left posterior cerebral artery.

Microscopic Observations.—Sections of the left temporal lobe showed congestion of the pial blood vessels with slight perivascular hemorrhage. The cortical ribbon displayed many small hemorrhages, mostly around congested capillaries, and many of the nerve cells had undergone ischemic changes. The white matter showed only a few scattered petechial hemorrhages and gave evidence of a moderate degree of edema.

Fig. 3 (case 1).—Cortical perivascular hemorrhage and relative sparing of the white matter.

CASE 3.—*Fall, of undetermined severity, sustained by a chronic alcohol addict. Rapid development of signs of intracranial pressure and meningeal bleeding on left side. Operation: evacuation of epidural and subdural hematomas. Hemostasis incomplete. Four days' survival. Death following lumbar puncture. Autopsy: widespread changes of chronic alcoholism; recurrent epidural hemorrhage on left side; contrecoup injury over opposite frontal lobe; edema of left hemisphere; supracallosal and uncal herniation on left; infarction of left occipital lobe in distribution of both anterior cerebral and posterior cerebral artery.*

History and Course.—W. K., a chronic alcohol addict, aged 46, was found about 4 p. m. lying on the sidewalk, with his head resting against a stone step. He was unconscious but was not brought to the hospital until approximately six hours later. Examination on admission

showed flaccid paralysis of the right arm and leg; the pupils were small and equal, but the left pupil began to dilate shortly after admission. His blood pressure was 120 systolic and 70 diastolic seven hours after the injury and 140 systolic and 70 diastolic eight hours after, at which time neurosurgical consultation was requested.

Examination at that time showed that he was deeply comatose and did not react to stimuli; breathing was irregular and rapid. There was a large, tense swelling in the left parieto-occipital region, with suggestion of an underlying cracked pot sound. The left eye was open and the right closed; there was no obvious weakness of the face. The right pupil measured 3.5 mm. and the left 5.5 mm., and neither reacted to light. The extraocular move-

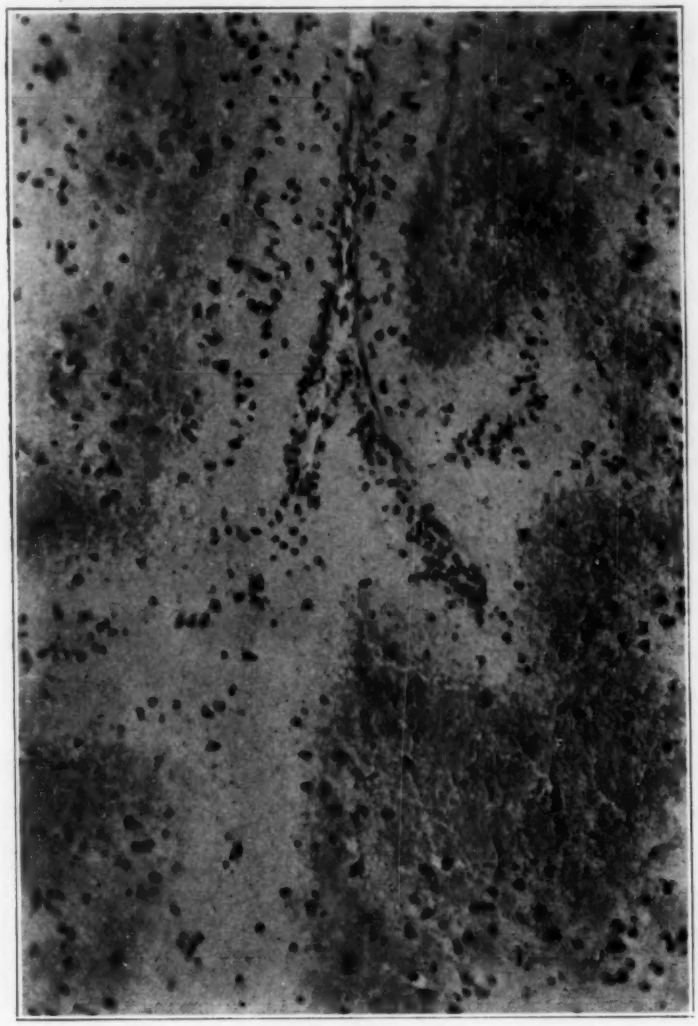

Fig. 4 (case 1).—Perivascular cuffing and necrosis.

ments could not be tested; the fundi were normal. It was noted that the patient was generally spastic and that the neck was stiff. On one occasion there was a suggestion of a bout of decerebrate rigidity. The deep reflexes were difficult to elicit, except for the right arm jerks. The abdominal reflexes were absent; the plantar responses were not remarkable. The general physical examination showed nothing of note.

He was taken directly from the receiving ward to the operating room, where a subtemporal decompression was made on the left side and a large, solid epidural clot was evacuated. The dura was then opened, and a subdural clot, 25 to 30 cc. in amount, was evacuated. There were considerable underlying damage to the brain and maceration of the cortex. The wound was closed in layers, and a Penrose drain was brought out through a separate stab wound.

The patient's postoperative course was stormy; his temperature ranged about 103 F.; the pulse rate varied from 100 to 120 a minute, and the respiratory rate was in the 40's. A lumbar puncture, done about thirty-six hours after operation, showed an initial pressure of 200 mm. of water and slightly yellow fluid.

On the third postoperative day the decompression area was full, but not extremely tense. The pupils had remained unequal and fixed since operation; the neurologic picture had altered little. On the fourth postoperative day the temperature ranged around 102 F., the pulse rate was 90 and the respiratory rate 40 a minute. Breathing was labored and grunting. He was

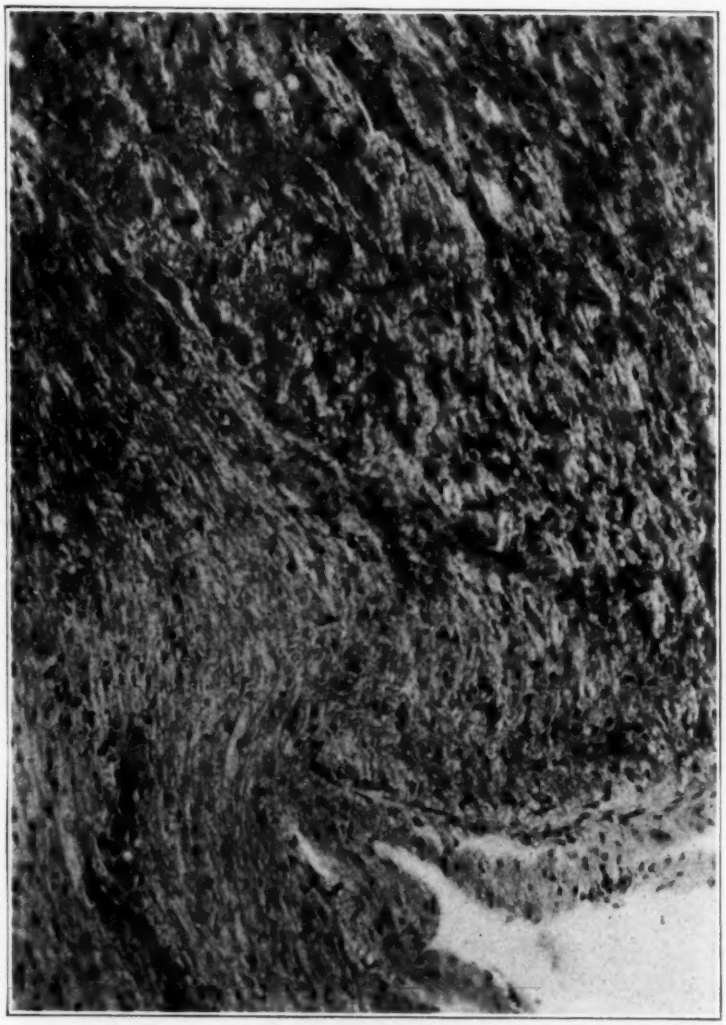

Fig. 5 (case 1).—Left oculomotor nerve, with hemorrhage at one side of the kinking about the posterior cerebral artery and absence of hemorrhage on the other side.

deeply comatose and did not respond to strong supraorbital compression. The left pupil was still larger than the right; the margins of the disks were visible; the plantar response could not be elicited on the right, and a normal one was suggested on the left. The blood pressure was 124 systolic and 80 diastolic. That afternoon lumbar puncture was done, after palpation of the decompression area, which was not tense. The initial pressure was 270 mm. of water. Despite this fact, 2.5 cc. of a yellowish fluid with a red tinge was removed, and one hour thereafter respiration stopped.

Gross Anatomic Observations.—An extensive epidural hemorrhage, measuring 8 by 10 cm. in diameter and 1 cm. in thickness, was encountered overlying the posterior parietal, upper temporal and anterior occipital regions. Inspection of the under surface of the brain showed

a lacerated area, measuring 2 cm. in diameter, at the base of the right frontal pole. Both temporal lobes were full. There was a large uncal herniation on the left, measuring 1.5 to 2 cm. in width and approximately 3 cm. in length. The third nerve had been sharply deviated and compressed by the herniation, the point of the angulation of the nerve lying at the midline. The corresponding point of the right third nerve lay 1 cm. to the right of the midline. The midbrain was shifted to the right for a distance of approximately 1 cm., and a definite cerebellar pressure cone was present.

The appearance of the multiple coronal sections may be seen in figure 8. The compression of the surface of the left hemisphere by the hematoma was evident. There were, in addition, a shift of the structures to the right and an obvious increase in the bulk of the white matter of the left hemisphere as compared with that of the right. In the gray matter of the first left temporal convolution there was a hemorrhagic area, measuring 1.3 cm. in width and 5 mm. in a dorsoventral direction. The gyrus was much compressed, and the gray matter

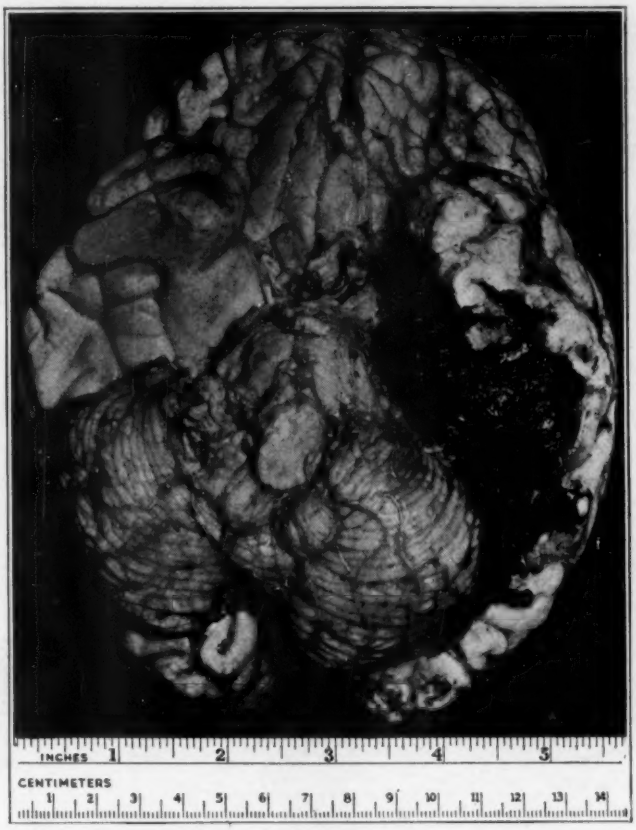

Fig. 6 (case 2).—Fulness of the left uncus and shift of the pons to the right.

was stained rather yellowish. In the second temporal convolution a similar, smaller hemorrhage involved the gray and the white matter. In the region of the left uncus perivascular hemorrhage involved the gray matter. In the more posterior sections swelling and hemorrhagic softening were evident in the lateral extent of the white fibers of the crus. In the occipital lobe was hemorrhagic softening along the mesial face of the lobe. The striking feature of that softening was its extension dorsally as well as ventrally, i. e., in the course of the terminal branch of the anterior cerebral artery as well as of the posterior cerebral artery, the usual site of hemorrhagic infarction in cases of trauma. In the search for an explanation of the softening in the distribution of the anterior cerebral artery, it became immediately evident that the shift of the left hemisphere under the free edge of the falx had produced a herniation of the supracallosal gyrus not at all dissimilar to the herniation of the uncal gyrus and that, presumably, the supracallosal herniation had interfered with the free flow of blood in the anterior cerebral artery by compression of the artery against the free edge of the falx.

Multiple sections through the brain stem and cerebellum showed nothing of significance.

Microscopic Observations.—Sections from the hemorrhagic regions of the left temporo-occipital lobe disclosed a great number of small hemorrhages in the gray matter, involving the cortical layers. The red cells were mostly well preserved and decolorized. There were striking congestion of the larger pial veins and capillaries and distention of the cortical capillaries, which were engorged with blood and surrounded by cuffs of red and white blood cells.

The nerve cells in these areas showed ischemic degeneration. The loss of nerve cells was such as to interfere with the cytoarchitectonics of the cortex. There was little or no glial

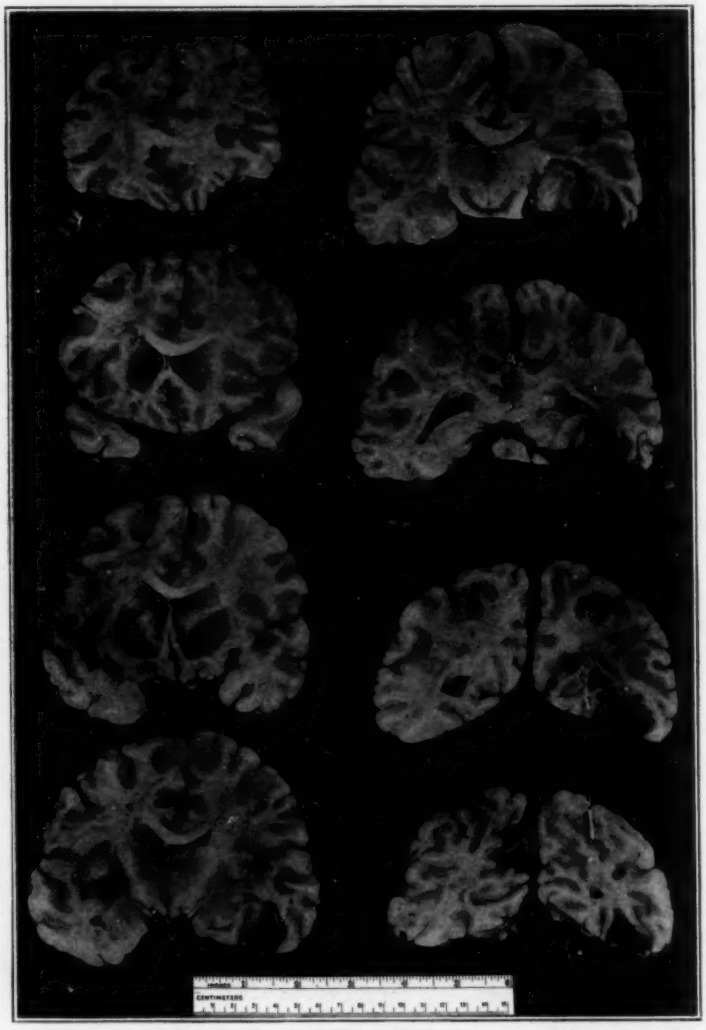

Fig. 7 (case 2).—Shift of the ventricular system, due to edema of the left hemisphere, and infarction in the course of the left posterior cerebral artery.

reaction. The white matter displayed evidence of edema and diffusely scattered perivascular hemorrhages.

Case 4.—E. H., a man aged 51, with hypertension, fell while drunk, at 10 p. m. on Jan. 31, 1942. When he failed to respond by 5 a. m. the next morning he was brought to the hospital. Examination showed a small occipital abrasion and right hemiparesis. The blood pressure was 240 systolic and 70 diastolic, the pulse rate 140, the respiratory rate 60 and the temperature 103.6 F. Lumbar puncture showed an initial pressure of 160 mm. of water; the fluid was bloody. The differential diagnoses of intracranial hemorrhage and intracranial

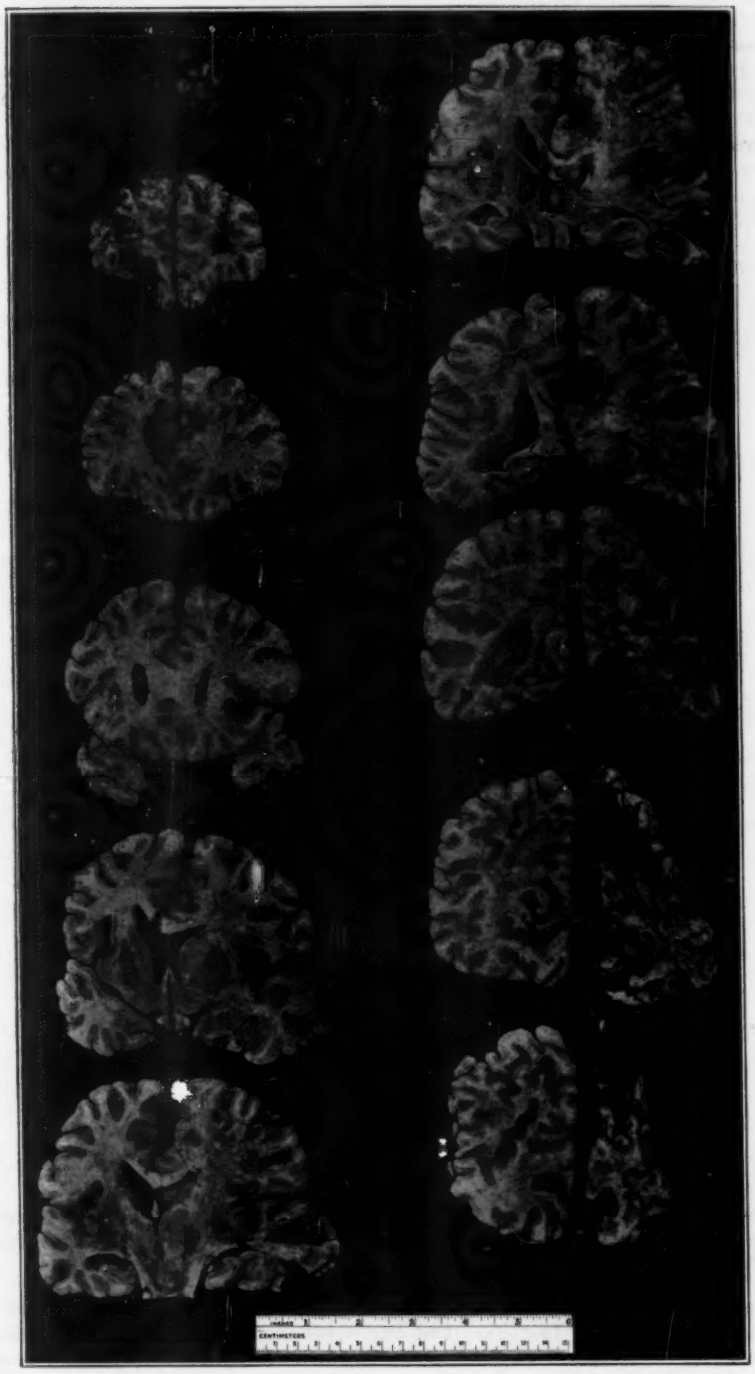

Fig. 8 (case 3).—Epidural and subdural hematomas on the left side. Note the shift of the brain from left to right, particularly the twin shifts of the supracallosal gyrus and the uncus, with the production of infarction in the distal distribution of both the anterior and the posterior cerebral artery.

injury were considered. Operation was decided against. A second lumbar puncture revealed an initial pressure of 310 mm. of water; 25 cc. of a very bloody fluid was removed; the final pressure was 150 mm. Death occurred nine hours after admission to the receiving ward and two and a half hours after the second lumbar puncture. Autopsy revealed fracture of the occipital bone and of the posterior clinoid processes; widespread subdural hemorrhage, measuring 3 to 5 mm. in thickness, over both frontal lobes and the right temporal lobe, and contusion of both frontal lobes. There were infarction in the distribution of the right posterior cerebral artery and changes suggestive of reduction in the collateral circulation of the right anterior cerebral artery.

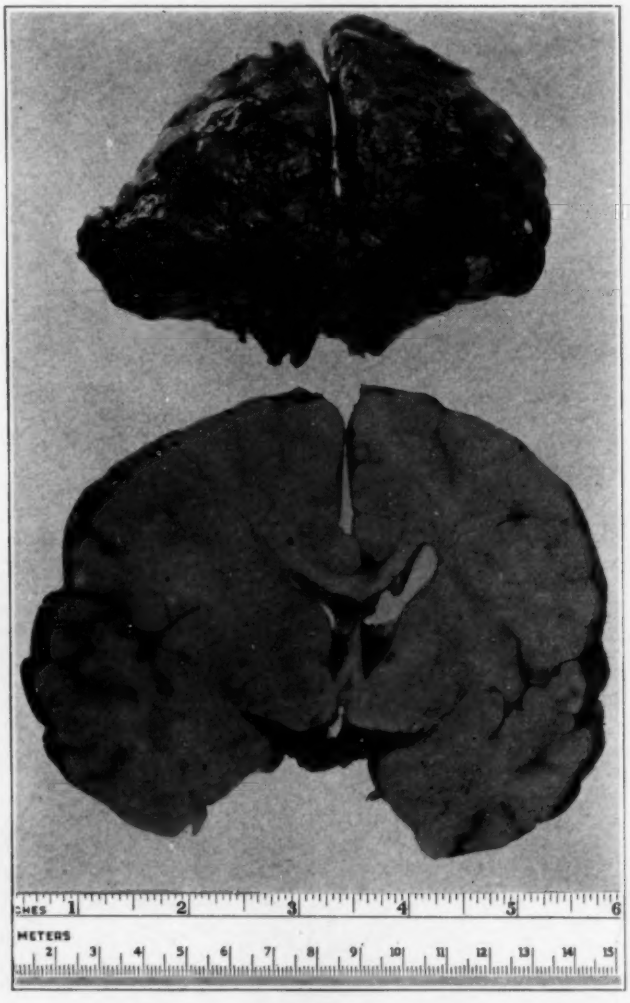

Fig. 9 (case 4).—Subdural hematoma overlying both frontal lobes. The supracallosal herniation on the right is well shown; the herniation of the right uncus is not clear in this block.

Gross Anatomic Observations.—Over both frontal lobes was noted a collection of blood measuring 5 cm. in thickness (fig. 9). The gyri were moderately flattened and the sulci somewhat narrowed. At the base there were considerable subarachnoid and subdural blood and an underlying laceration of the right frontal lobe. A prominent uncal herniation on the right measured 7 to 8 mm. in width and 2 cm. in anteroposterior direction. The under surface of the right temporal and occipital lobes showed brownish discoloration, indicative of infarction. The right supracallosal gyrus was displaced and herniated under the free edge of the falx. Moderate arteriosclerosis of the basilar vessels, without plaque formation, was observed.

Cross sections through the brain showed extensive infarction throughout the distribution of the right posterior cerebral artery, as shown in figure 10. The right occipital lobe was

slightly swollen. There was hemorrhagic infiltration of the gray matter of the inferior and mesial portions of the right occipital lobe. The widespread swelling and infarction noted in figure 10 must mean at least partial impairment of circulation in the course of the anterior cerebral artery, as well as in that of the posterior cerebral artery, the impairment resulting from the supracallosal herniation.

Multiple sections made through the brain stem showed an area of gross hemorrhage involving the major portion of the mesencephalon (fig. 10). The sections of the lower part of the brain stem were normal.

Microscopic Observations.—Sections were taken from the left occipital and temporal lobes and from the brain stem. The significant changes were twofold, those in the white matter and those in the cortical ribbon.

The white matter presented the typical microscopic picture of cerebral edema. The changes were characterized by the alveolar, sievelike appearance of the nerve tissue, marked distention

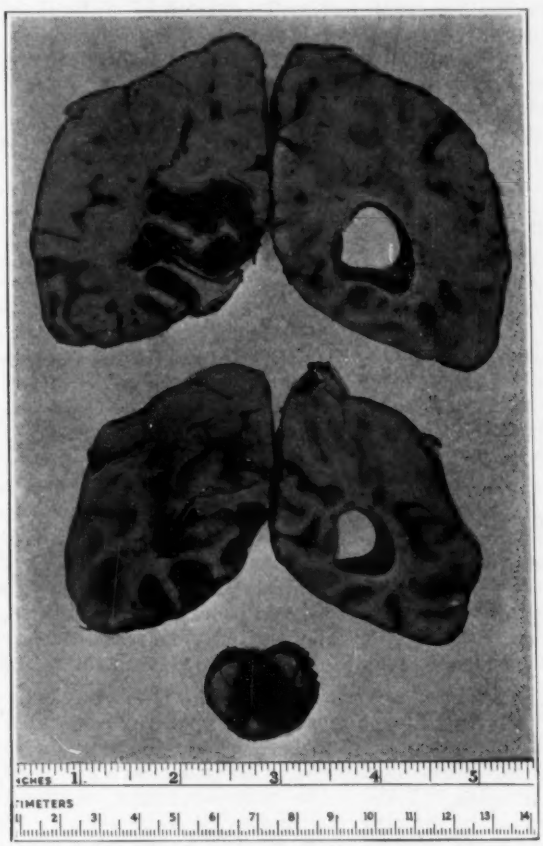

Fig. 10 (case 4).—The upper block shows changes probably confined to the distribution of the right posterior cerebral artery. The middle block shows extensive change in almost the entire occipital lobe, suggesting that the collateral circulation by way of the right anterior cerebral artery may have been reduced by the herniation of the supracallosal gyrus.

of the pericellular and perivascular spaces and morphologic signs of alteration of the circulatory system, with an increase in permeability of the vessel walls. Many of the vessels showed perivascular accumulations of serous fluid.

The changes in the cortical ribbon were uniform. With low power magnification the entire gray cortex appeared infiltrated with multiple hemorrhages. There were gross dilatation of all the vessels, accumulations of large masses of red blood cells around the capillaries and arterioles and circumscribed areas of small hemorrhages scattered throughout the gray matter. The changes in the nerve cells were similar to those associated with cerebral hypoxia. The majority of the ganglion cells revealed shrinkage, loss of nuclear and nucleolar outlines and cytoplasmic changes, indicated by homogeneity of substance and dark staining. Satellitosis

was noted in some areas, and there was a falling out of ganglion cells, so that the normal architectural relationships were distorted. The glial reaction was minimal.

CASE 5.—*Severe injury to the head from assault. Development of coma, decerebrate rigidity and dilatation of the left pupil during next one and a half hours. Operation thirteen hours after injury: evacuation of epidural hematoma on left side. Persistence of decerebrate rigidity after operation. Death on fourth day. Autopsy: recurrent epidural hematoma on left side, infarction in distribution of left middle cerebral artery and hemorrhagic softening of brain stem.*

History and Course.—C. D., aged 50, was assaulted about 6 a. m. on Jan. 4, 1943. He walked a distance of some 50 feet (15 meters) and reported the injury to a fellow worker, who drove him to his home, where the patient remained conscious, though confused, for about an hour after the injury. He then lost consciousness over a half-hour period and was brought immediately to the hospital.

Examination showed multiple small lacerations behind the left ear and in the left occipital region. A hematoma in the left periorbital region increased appreciably during the first hour of observation. Fresh blood drained from the left ear, and blood was noted in the nasopharynx. The temperature was 98 F. and the blood pressure 160 systolic and 88 diastolic. He was comatose and displayed repeated bouts of decerebrate rigidity. The right pupil measured 2 mm. and the left 3.5 mm., and neither reacted to light. The deep reflexes were hyperactive throughout. The abdominal reflexes were absent, and the plantar responses were of the extensor type.

He was admitted to the ward at 9 a. m., three hours after his injury, at which time the temperature was 102 F., the respiratory rate 28 and the pulse 76 and irregular. Intranasal administration of oxygen was begun. Within three hours the temperature rose to 104.4 F.; the pulse rate remained in the 70's, and the respiratory rate was 28 a minute. The presence of an epidural clot was not suspected until the patient was seen by the neurosurgical consultant, at 5 p. m., and operation was begun at about 7 p. m., thirteen hours after the injury. A large epidural clot was evacuated on the left side, and a thin sheet of subdural blood was noted on the right. His condition was critical throughout the procedure, the systolic pressure dropping from 180 to 80, despite intravenous administration by the drip method of isotonic solution of sodium chloride, blood and plasma in abundant quantities. The blood pressure at midnight, two hours after the close of the procedure, was 90 systolic and 50 diastolic.

The patient never regained consciousness. On the second postoperative day the hemoglobin content of the blood was 12 Gm. and the white cell count 16,000 per cubic millimeter, and the urine gave a 1 plus reaction for albumin but was otherwise normal. The urea nitrogen of the blood at this time was 39 mg. per hundred cubic centimeters. Lumbar puncture, on the third postoperative day, revealed an initial pressure of 170 mm. of water. The fluid was opalescent and contained 6,100 red blood cells per cubic millimeter. The Wassermann reaction of the cerebrospinal fluid was negative, and the colloidal gold curve was negative. Death occurred on the fourth postoperative day. Necropsy was performed seven hours after death.

Gross Anatomic Observations.—A recurrent epidural clot, anteriorly placed and centering over the left frontoparietal region, was present. The ventral surface of the brain showed a tremendous herniation of the left temporal lobe over the free edge of the tentorium, the tentorial marking on the uncus measuring 2.8 cm. in the anteroposterior direction and the greatest width of the herniation being 1.1 cm. The anterior extent of the uncal herniation was extreme and was embraced by the curving middle cerebral artery. The herniation was so prominent that it seemed likely, in view of later observations, that the middle cerebral artery was compressed in its course against the bony rigidity of the sphenoid wing. The relationships of the posterior cerebral artery in its course about the kinked third nerve did not appear remarkable.

The lateral surface of the left hemisphere showed a brownish hemorrhagic discoloration throughout the entire extent of the distribution of the left middle cerebral artery, and the underlying cerebral substance was soft to touch. In the midportion of the third temporal convolution was a superficial loss of substance.

Multiple coronal sections through the hemispheres showed local hemorrhagic softenings in the herniated uncus of the temporal lobe and softening of the left hemisphere throughout the distribution of the middle cerebral artery, associated with hemorrhagic softening of much of the cortical ribbon in the same distribution. In addition, in the brain stem hemorrhagic softening was noted in the area subjacent to the substantia nigra. The red nuclei were both clearly defined, the left appearing swollen. There was to be seen edema of the tegmen of the pons, especially in the region of the decussation of the brachia conjunctiva, with discoloration and diffuse loss of the gross architectural arrangement of the region.

Microscopic Observations.—Throughout the left hemisphere, including the hypothalamus, and in the brain stem there were observed maximal dilatation and congestion of capillaries and small veins. The walls of many of the vessels showed beginning degeneration. There was increased permeability of the vessels, manifested by the extravasation of large amounts of serous fluid into the perivascular spaces and adjacent nerve tissue. These changes were especially evident within the brain stem and the hypothalamus, though present to a lesser degree in the white matter of the cornu ammonis and of the occipital lobe. More extreme vascular alterations were seen in the cortical ribbon of the left perisylvian area, where many of the maximally distended vessels were surrounded by small perivascular hemorrhages, resulting in the typical picture of hemorrhagic softening.

Ischemic changes, roughly proportional to the degree of vascular disturbance, were noted in the nerve cells of the cortical ribbon supplied by the middle cerebral artery.

Additional evidence of disturbed blood supply was the alveolar, sievelike appearance of the parenchyma of the nervous system, changes which were particularly prominent in the white matter of the temporal lobe and in the brain stem and which were regarded as representing a severe degree of edema. Scattered in the brain stem and the hypothalamus were circumscribed areas of tissue necrosis, devoid of glial reaction in most instances, although occasionally areas more severely affected showed clasmatodendrosis and the formation of very occasional gitter cells. Occasional small circular hemorrhagic areas were observed, usually disclosing in their center a small congested vein with advanced degeneration of the wall. These changes were similar to, but of lesser degree than, the changes noted in the left hemisphere. It should be particularly noted that the vessels at the base of the brain were soft and showed neither gross nor microscopic evidence of arteriosclerosis.

CASE 6.—*Boy aged 16 years, thrown from a bicycle at 6 p. m. Transient loss of consciousness. No significant neurologic signs at 7 p. m. At 9 p. m. drowsiness and right-sided headache. At 10 p. m. coma and dilatation of right pupil. Head held to right, and accentuation of deep reflexes, more so on right side. Bilateral Babinski response and intermittent decerebrate rigidity. Operation six hours after injury: incomplete evacuation of epidural clot on right. Continued coma; death at the end of a week. Autopsy: terminal lobular pneumonia; bilateral fractures of temporal bone and recurrent epidural hematoma on right side. Hemorrhagic softening (infarction) of right temporo-occipital lobe and softening of central gray matter of the midbrain shown in sections.*

History and Course.—J. H., a lad of 16, fell from his bicycle at 6 p. m., on April 2, 1942, striking the right side of his head. Consciousness was lost temporarily, but on admission to the hospital, at 7 p. m., he was oriented and cooperative and complained of pain over an abrasion on the right side of the forehead. There were conjunctival hemorrhage on the left side and a periorbital hematoma on the right. The pupils were of equal size and reacted well. There was no defect of the visual fields; the fundi were normal, and nothing else of significance was detected on neurologic examination.

He reached the ward at 9 p. m., at which time he was a little drowsy and complained of right hemicephalalgia. At 10 p. m. he was found in comma and exhibited decerebrate rigidity. The right pupil was dilated, and the head was held to the right. The deep reflexes were accentuated, more so on the right side than on the left, and there were bilateral extensor responses on plantar stimulation. A diagnosis of epidural hemorrhage on the right side was made, and he was taken to the operating room as quickly as possible.

Operation was begun at midnight, and an extensive extradural hemorrhage was encountered, which was difficult to control. The temperature rose to 106.6 F., and the pulse rate to 160 a minute.

The decerebrate rigidity persisted despite the giving of phenytoin sodium and the intratracheal administration of oxygen, continued over many days. Intravenous injections of fluid, administration of vitamins and frequent blood transfusions were employed, but he failed to regain consciousness and died at the end of a week.

The Wassermann reactions of the blood and the spinal fluid were negative. The hematocrit reading on April 8 was 31.3 volumes per cent. The plasma proteins measured 6.66 Gm., and the chlorides of the blood 725 mg. per hundred cubic centimeters, and the carbon dioxide–combining power was 51 volumes per cent. A lumbar puncture on April 8, 1942, the day before death, showed a pressure of 180 mm. of water, xanthrochromic fluid and 6 white blood cells and 600 red blood cells per cubic millimeter. The total protein of the fluid was 86 mg. per hundred cubic centimeters.

Autopsy showed, in addition to the cerebral lesions, confluent lobular pneumonia and acute bronchitis. There were bilateral linear temporal fractures.

Gross Anatomic Observations.—A recurrent epidural hemorrhage, measuring 6 cm. in diameter and 1 cm. in thickness, was noted on the right side. Inspection of the under surface

of the brain showed considerable broadening of the right temporal lobe and herniation of the uncus. The cerebral substance was fairly soft to touch. The herniation measured 1 cm. in width and 2.5 cm. in length. There was grayish brown discoloration of the under surface of the occipital lobe, indicative of hemorrhagic infarction. The right third nerve was kinked around the posterior cerebral artery. This was true also of the left nerve, to a lesser degree. The cerebellum showed fulness of the tonsillar region, but not a prominent herniation. The vessels at the base were soft and of normal distribution.

Coronal sections of the brain revealed the following changes: a shift of the midline to the left; general congestion of the vessels, with petechial hemorrhages most evident in the corpus callosum; fulness of the right hemisphere, especially in the temporal region, and hemorrhagic softening of the right temporo-occipital lobe in its central mesial portion, with sparing of the calcarine cortex. In addition, there were pinkish discoloration of the central gray matter of the midbrain and diffuse softening of the tissue in this vicinity. The remaining sections through the brain stem and cerebellum revealed nothing of note.

Microscopic Observations.—The cortical ribbon of the right uncus, as well as that of the occipitotemporal area, showed a typical picture of hemorrhagic softening. Small hemorrhages were scattered diffusely throughout the various cortical layers. Red blood cells were fairly well preserved and fresh in appearance. Most of the capillaries were engorged with blood; many were surrounded with cuffs of polymorphonuclear leukocytes and a small number of gitter cells. The majority of the ganglion cells were lost; the remainder showed signs of ischemic degeneration. Reaction of the macroglia was minimal.

In sections through the level of the junction of the pons and mesencephalon, circumscribed softening of the central gray matter was seen involving the locus caeruleus, the dorsal nucleus of the raphe and the middle portion of the right brachium conjunctivum.

COMMENT

HISTOLOGIC CONSIDERATIONS

It was suggested in the introduction that several features of these cases would be stressed, and each of these factors will herewith be discussed.

Unilateral Edema of the Temporal Lobe as a Factor in Uncal Herniation.—The explanation of the shift of the temporal uncus over the free edge of the tentorium seems simple and direct in the case of either subdural or epidural hemorrhage. The investigations of Reid and Cone, in which the introduction of saline solution into the extradural space in one series of experiments and of moistened saraka seeds or gum tragacanth into the subdural space in another series caused signs of disturbance of the third nerve and infarction of the posterior cerebral artery, suggested that mere mechanical displacement by a space-consuming lesion was an adequate explanation of the reduced flow in the posterior cerebral artery.

While this simple mechanism may apply in certain instances, we have observed in our cases of injury to the brain that the temporal lobe may be full and swollen. While this is a common observation in cases of tumor, as indicated by Jefferson, its occurrence in association with injuries to the head has not been stressed. In recent papers [8] dealing with post-traumatic cerebral edema and hemorrhage, we have shown instances of unilateral swelling of the brain subsequent to trauma. Such swelling must contribute to the herniation of the uncus, with its resultant compression of the posterior cerebral artery. In the cases cited in the present paper histologic analysis has disclosed the presence of edema of the temporal lobe on the side of the uncal herniation. Histologic changes were characterized by vascular stasis, distention of the perivascular spaces, transudation of red blood cells and serum into the nerve tissue about the blood vessels, distention of perineuronal spaces and an alveolar, sievelike appearance of the nerve parenchyma. We believe that

8. Evans, J. P., and Scheinker, I. M.: Histologic Studies of the Brain Following Head Trauma: (*a*) I. Post-Traumatic Cerebral Edema, to be published; (*b*) II. Post-Traumatic Petechial and Massive Intracerebral Hemorrhage, to be published.

edema plays an important contributory role in the production of uncal herniation and that, as indicated in our earlier papers, this edema may be profound. Actually it may be profound on the side opposite the meningeal hemorrhage. And that edema alone may on occasion be the important element in the shift of the uncus seems to be indicated by Maltby's [9] review of our subdural hematoma material. Among 7 cases associated with changes in the visual fields there was 1 case, unconfirmed by postmortem examination, in which the loss of the homonymous field (presumably dependent on dysfunction of the occipital lobe) was on the side of the hematoma as disclosed at operation, an observation suggesting that edema of the opposite hemisphere was responsible for the hemianopia. In a second case, verified at autopsy, there was gross and microscopic evidence of bilateral infarction of the posterior cerebral artery. The changes, as might be expected, were more extensive on the side on which the hematoma was noted at operation.

Relation of the Swollen Occipital Lobe to the Herniation of the Temporal Lobe.—In the acute stages of infarction of the occipital lobe there is swelling of the lobe. Inasmuch as it is confined to the posterior portion of the rigid middle fossa, and inasmuch as the falx, in the adult, is a relatively immobile structure, it is obvious that there must be a tendency for the occipital lobe to contribute to the displacing effect on the mesial portion of the temporal lobe. The displacement is, of course, accentuated by the presence of the clot itself, which may be sizable.

It should be mentioned in passing that recession of the edema may occur, with resultant subsequent atrophy of portions of the occipital lobe. Though we have not seen pathologic evidence of such changes in association with head injury, it has been described in association with tumor (Moore and Stern), and we have repeatedly seen recession in visual field defects in cases of head injury following evacuation of a subdural hematoma, these cases having previously been reported by Maltby.

Nature of the Mechanism Responsible for Infarction of the Occipital Lobe.—The infarctions in the occipital lobe associated with uncal herniation have rather generally been described as involving the calcarine cortex, and it has therefore been concluded that the changes resulted from disturbances in flow in the posterior cerebral artery. It has been postulated that the herniating uncus has shifted the posterior cerebral artery against the rigid third nerve, which courses about the posterior cerebral artery, and that the flow in the posterior cerebral artery is thereby reduced.

Another observation, however, deserves additional comment before this explanation is accepted. The histologic features of the cases presented here are those of an early stage of hemorrhagic softening involving the cortical ribbon. There is not, as pointed out by Cobb [10] in 1937, general agreement as to the factors responsible for "red infarction," as opposed to "white infarction." In the same year one of us (J. P. E.) with McEachern [11] reported that sudden experimental occlusion of the middle cerebral artery of the monkey resulted in white infarction. We were not able to devise a satisfactory experimental method of occluding a vessel slowly, but we suggested on theoretic grounds that possibly the preservation

9. Maltby, G. L.: Visual Field Changes and Subdural Hematomas, Surg., Gynec. & Obst. **74**:496, 1942.

10. Cobb, S.: Cerebral Circulation: A Critical Discussion of the Symposium, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:719, 1938.

11. Evans, J. P., and McEachern, D.: The Circulatory Changes in Cerebral Vascular Occlusion and in Cerebral Cicatrization, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**: 379, 1938.

of some blood flow in the course of the affected artery might make it possible for diapedesis to occur through vessels weakened by hypoxia and that in this fashion red infarction occurred.

Histologic study of the present cases suggests another explanation, for the alterations are similar to those seen in hemorrhagic infarction of the cerebral cortex occurring in association with thrombosis of the dural venous sinuses. Such changes were reported by Bailey and Hass [12] in their study of 30 instances of thrombosis of the dural sinuses in infancy and childhood. In 21 of the cases they noted hemorrhagic softening and necrosis in the gray matter. Similar histologic changes were observed by Byers and Hass [13] in a large group of cases of thrombosis of the venous sinuses. Cobb and Hubbard,[14] likewise, demonstrated hemorrhagic softening in association with venous occlusion.

We have seen both experimental [11] and clinical [8a] evidence that the edema occurring within the zone of supply of a cerebral artery may lead to a shift of the midline structures of the brain, an effect indicating undue confinement of the swollen hemisphere within the limits of the half-skull. That this should interfere with venous return in the major vessels, possibly even in kinking of the larger veins as they cross the subdural space, seems not unlikely. We propose this view for consideration. The shift of the hind end of the third ventricle and the upper end of the aqueduct of Sylvius that occurs in the more extreme cases serves to heighten the increasing intracranial pressure by causing a block at the aqueduct.[6] It may be that the veins of Galen are also subjected to compression. These, then, are elements which tend still further to impede venous outflow from the hemisphere, and we therefore believe that the added element of interference with venous return is essential for the development of red, or hemorrhagic, infarction. But it seems that disturbance in the arterial flow must be the condition precedent to venous obstruction.

Occurrence of Hemorrhagic Infarctions in Distribution of Arteries Other Than the Posterior Cerebral.—De Veer and Browder,[15] in a case of injury to the head, observed infarction in the course of the middle cerebral artery. This they attributed to rupture of the wall of the artery near its origin. Such a lesion may sometimes serve as an explanation of the hemorrhagic infarction. Actually, in 2 cases in our own series infarction was present in the course of the anterior cerebral artery, in combination with that of the posterior cerebral artery, and in our fifth case there was infarction in the course of the middle cerebral artery.

The mechanism of infarction described in the cases of infarction of the posterior cerebral artery, namely, the reduction in flow in the posterior cerebral artery resulting from kinking of this vessel about the relatively rigid third nerve, which occurs in association with the uncal herniation, suggests a similar explanation for the other major cerebral arteries. Indeed, reference to figure 8 shows that a wholly comparable set of circumstances develops with infarction of the anterior cerebral

12. Bailey, O. T., and Hass, G. M.: Dural Sinus Thrombosis in Early Life: I. The Clinical Manifestations and Extent of Brain Injury in Acute Sinus Thrombosis, J. Pediat. **11**:755, 1937.

13. Byers, R. K., and Hass, G. M.: Thrombosis of the Dural Venous Sinuses in Infancy and in Childhood, Am. J. Dis. Child. **45**:1161 (June) 1933.

14. Cobb, S., and Hubbard, J. P.: Cerebral Hemorrhage from Venous and Capillary Stasis: Report of Five Cases, Am. J. M. Sc. **178**:693, 1929.

15. De Veer, J. A., and Browder, J.: Post-Traumatic Cerebral Thrombosis and Infarction: Report of a Case and Discussion of Its Bearing on the Problem of Immediate and Delayed Post-Traumatic Apoplexy, J. Neuropath. & Exper. Neurol. **1**:24, 1942.

artery, for it is evident that in case 3 the supracallosal gyrus has been forced under the lower edge of the falx and it is likely that the displacement resulted in compression of the anterior cerebral artery against the free edge of the rigid falx.

In case 5, that of infarction of the middle cerebral artery it is likely that the remarkably large and anteriorly placed uncal herniation compressed the middle cerebral artery against the sphenoid wing. The rarity of this mechanism suggests that some unusual circumstance was responsible for it. Possibly the rather anteriorly placed hematoma may have contributed to the relatively anteriorly placed uncal herniation. We have no other explanation to offer at present.

Changes in the Brain Stem.—The explanation by Moore and Stern of the hemorrhagic alterations seen in the brain stem has previously been noted. These authors described the hemorrhages as being periarterial, or at least periarteriolar and expressed the opinion that they were related entirely to the arterial side of the circulation. They suggested that with increasing supratentorial pressure reflex alterations in the blood pressure occur, resulting in an increased head of arterial pressure, which seeks to provide adequate oxygenation of the supratentorial neurons. They pointed out, however, that in the subtentorial region the intracranial pressure may be relatively low, and they argued therefore that there is a predisposition to hemorrhage in the rostral end of the brain stem, the blood stream entering the supratentorial fossa by way of the basilar artery and meeting with undue resistance. Here the hemorrhages are likely to occur. However, why arterial pressure should increase in compensatory fashion when the increase in intracranial pressure is limited to the supratentorial chamber as they postulated, is not clear.

We argue that hemorrhagic changes are not solely of arterial origin but, again, are a reflection of interference with free venous outflow, because of the postulated compression of the veins draining the upper area of the brain stem. In other words, we postulate the same mechanism for the hemorrhages in the brain stem as for the changes in the occipital lobes, rather than assume two processes. We believe we have seen evidence in our autopsy material of interference with venous outflow in the brain stem, but the mechanism is one which will require further study of herniating and compressed cerebral structures.

Degrees of Change in the Brain Stem.—In the literature, stress seems to be laid on the occurrence of hemorrhage in the brain stem, and relatively little attention has been paid to lesser degrees of change, which may well be of functional significance. From the clinical point of view these changes may be reversible, whereas when frank hemorrhage has occurred death may soon result. In case 6 edema of the brain stem appeared to be present even though frank hemorrhage was not observed. Case 6 offers histologic evidence of such a condition. It may well be that in cases of an incomplete picture of transection of the brain stem in which there is clinical recovery such edematous changes exist as the histologic counterpart.

CLINICAL CONSIDERATIONS

The papers of many authors have contributed to a fuller understanding of the physiologic disturbances occurring in cases of epidural and subdural hematoma. One might cite as examples the paper of Rand [16] on the significance of the dilated pupil, that of Jefferson [17] on the occurrence of decerebrate rigidity, the articles

16. Rand, C. W.: Significance of Dilated Pupil on Homolateral Hemiplegic Side in Cases of Intracranial Hemorrhage Following Head Injuries: Report of Seven Cases, Arch. Surg. **18**:1176 (April) 1929.

17. Jefferson, G.: Bilateral Rigidity in Middle Meningeal Hemorrhage, Brit. M. J. **2**:683, 1921.

of Munro[18] on the variability of clinical signs (and hence the need of being "hematoma conscious" and of placing exploratory burr openings) and, finally, the many papers already referred to in this presentation which point out the occurrence of infarction of the posterior cerebral artery and hemorrhages of the brain stem. The clinical features are variable, and a protean, not a hard and fast, picture may be drawn.

Our own clinical experience suggests that exploration is demanded in any case in which, on the basis of the history or the physical findings, an injury to the head is suspected and deepening coma (sometimes unexplained rising temperature) and/or localizing signs are present. "Localization necessitates operation" is a good axiomatic rule to follow. Among localizing signs may be cited paresis of one side of the face or body, which may be manifested by obvious weakness, loss of tone or reflex changes, particularly the appearance of a Babinski response. Dysphasia, often confused on superficial examination with mental disorientation, may be a particularly valuable sign. Attention has already been drawn by Maltby to the value of confrontation tests in determination of visual fields. Surprisingly, he found that in 11 per cent of our series of 62 cases of verified subdural hematoma encountered during a four year period it was possible to demonstrate visual field defects; actually, in an attempt to lateralize the clot the changes in the visual fields in this small series were twice as valuable as the pupillary signs. It must be emphasized, again, that the appearance of changes in the visual fields means that serious circulatory alterations have already occurred, which, if not relieved by immediate evacuation of the clot, may well lead to irreversible changes and to death.

There are at least two explanations of the dilated pupil seen in some cases of cerebral compression. One is that afforded by Reid and Cone, who suggested that it is the result of pull on the third nerve as it kinks about the posterior cerebral artery. They demonstrated hemorrhage in the nerve as the result of such traction, and in our first case similar changes were shown. The second explanation is that of hemorrhage in the vicinity of the nuclei of the third nerve. The latter explanation is probably the valid one in instances in which both pupils become fixed and dilated. The gravity of these extreme pupillary changes is generally recognized, and it is almost a rule that the presence of fixed, dilated pupils precludes recovery.

By all odds, the gravest prognostic sign is the appearance of decerebrate rigidity, which in 2 of the cases cited in this presentation developed while the patient was under observation but was not recognized immediately as an indication for urgent evacuation of the clot. Too much emphasis cannot be laid on the imperative need of speed when this sign appears; in many instances it may mean that irreparable harm has already occurred.

The best type of exploration to be employed is a matter of debate. We prefer to use bilateral subtemporal burr openings in cases of the acute type. These openings can readily be enlarged if an extradural clot or a solid subdural accumulation of blood is encountered on one or both sides. In cases of the subacute and chronic forms bifrontal and bioccipital openings are placed. If these openings reveal nothing and a clot is still suspected, bilateral subtemporal openings are made of sufficient size to permit adequate exploration of the subdural space, for subdural hematomas may be aberrantly situated.[19] The Light head rest is employed, and the entire head is prepared and draped, so that ready access may be had to any

18. Munro, D.: Craniocerebral Injuries: Their Diagnosis and Treatment, New York, Oxford University Press, 1938.

19. Aring, C. D., and Evans, J. P.: Aberrant Location of Subdural Hematoma, Arch. Neurol. & Psychiat. **44**:1296 (Dec.) 1940.

area without the need of redraping. We have found in some instances that the occipital openings may be of value for later ventriculographic studies in problem cases.

Encephalographic examination is, in our opinion, interdicted. Further, we believe that lumbar puncture is potentially a hazardous procedure. We think it contributed directly to the death of the first patient and that it may have played a role in the death of the third and fourth patients. Hence, when employed, it must be used intelligently, and preferably only immediately before operation. It must be recognized, also, that the pressure observed at lumbar puncture may not be a true index of the supratentorial pressure, and hence may mislead one into a false sense of security.

The surgeon faced with the practical matter of dealing with head injuries may well ask what additional therapeutic leads are to be derived from laboratory studies such as those embodied in this report. Aside from their emphasizing the progressive vicious development of infarction of the cerebral arteries, and thus stressing the value of prophylaxis through early evacuation of the clot, it must be frankly admitted that in the present state of knowledge such studies are of slight aid. Until more is learned of the physiologic and chemical basis of the histologic changes described, not much other than prompt surgical intervention can be recommended with sound support. The maintenance of an adequate airway is imperative, and in skilled hands the introduction of an endotracheal tube when the patient is first seen in the receiving ward may be of the greatest value in handling the emergency stage. Such a tube permits both suction of material from the bronchi and effective administration of oxygen. Later the B-L-B inhalation apparatus, or a posteriorly placed nasal catheter, may be substituted. The use of oxygen is probably of particular value when the patient is suffering from shock or from hyperthermia.

We now employ hypertonic solutions rather infrequently, believing that they may interfere with the physiologic activity of the vessel wall and may possibly facilitate formation of edema. This opinion has not been confirmed, but we limit the use of hypertonic solutions to emergency cases in which temporary relief of pressure is imperative for even the temporary maintenance of life. Whether the administration of endocrine preparations to alter capillary permeability [20] will prove of value remains to be demonstrated clinically.

SUMMARY

Attention is called to the incomplete clinical understanding of the edema and hemorrhage resulting from trauma to the brain and of the associated disturbances in circulation of the cerebrospinal fluid.

Six cases of epidural and subdural hematoma in which the mesial portion of the temporal lobe was displaced over the free edge of the tentorium are described, including the clinical history and the gross and histologic changes in the brain.

In 2 of these cases classic infarctions in the distribution of the posterior cerebral artery were displayed. In 2 cases, in addition to the well known uncal herniation, herniation of the supracallosal gyrus under the free edge of the falx was present. There resulted therefrom infarction in the course of the anterior cerebral artery, in addition to the infarction in the course of the posterior cerebral artery related to the uncal herniation.

In the fifth case, in which the uncal herniation was unusually full, interference with flow in the middle cerebral artery resulted, producing infarction in the dis-

20. Prados, M.: Personal communication to the authors.

tribution of that vessel, in association with a lesser degree of infarction in the course of the posterior cerebral artery.

In the first, fourth, fifth and sixth cases there were associated histologic changes in the brain stem, and physiologic changes were also present, as indicated by signs of decerebration of varying degrees.

The role of edema in the production of the herniations is emphasized.

It is argued, on histologic grounds, that reduction of flow in any one of the major cerebral arteries is of itself not an adequate explanation of the resultant red infarction of portions of a hemisphere. To the arterial disturbance must be added interference with free venous outflow from the affected area.

The same mechanism, reduction in arterial inflow and interference with venous outflow, is thought to be an adequate explanation of the hemorrhages in the brain stem so often seen in association with epidural and subdural hematomas.

Attention is drawn to the importance of edema of the brain stem, a precursor of hemorrhage.

The clinical picture presented by these cases is discussed, and an effort is made to draw practical lessons from the information derived from consideration of the histologic picture. Most important is the early evacuation of the clot. Decerebration is a bad prognostic sign. Administration of oxygen and suction of material from the bronchi by an endotracheal tube are important steps in emergency treatment. The value of hypertonic solutions is thought to be questionable. Lumbar puncture, if employed at all, must be used with full realization of the mechanical factors and the risks involved.

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STUDIES IN DISEASES OF MUSCLE

XIV. PROGRESSIVE MUSCULAR ATROPHY OF PERONEAL TYPE ASSOCIATED WITH ATROPHY OF THE OPTIC NERVES; REPORT ON A FAMILY

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Progressive peroneal muscular atrophy associated with bilateral atrophy of the optic nerve is of rare occurrence. Only 6 observers appear to have reported cases of this type. Twenty-six years after his original description of peroneal muscular atrophy Tooth [1] stated that he never had seen this symptom complex. Vizioli,[2] in 1879, described a family in which the father, aged 59, and his 2 sons, aged 26 and 6 years, presented atrophy of the muscles of the calves; the hands were affected later in 2 of the patients. Both the father and the older son had progressive impairment of vision and finally became totally blind. Ophthalmoscopic examination showed bilateral optic nerve atrophy. The younger brother apparently retained normal vision, but he was examined only during the early stages of the disease.

Similar cases were reported by Sainton,[3] Gordon,[4] Ballet and Rose,[5] Taylor [6] and Krauss.[7] Sainton reported the occurrence of progressive muscular atrophy and optic nerve atrophy of many years' duration in an 84 year old man, whose grandson had similar muscular wasting. A brother of the patient, reported by Ballet and Rose, was said to have the same disease. In all of the cases the muscular atrophy was of the Charcot-Marie-Tooth type.

While it is possible that the simultaneous occurrence of muscular wasting and optic nerve atrophy was incidental, the uniformity of the clinical picture and the high familial incidence make it more likely that the muscular and ocular changes represented either a definite clinical syndrome or a distinct type of Charcot-Marie peroneal muscular atrophy. For this reason, publication of the present report of a family appears justified. Two brothers showed all the features of the disease, while a sister had bilateral optic nerve atrophy with a condition resembling disseminated sclerosis.

REPORT ON FAMILY

The 6 siblings and other members on whom information could be obtained are represented in figure 1. The parents and grandparents are said to have been without muscular or visual disability. It is of interest that the affected members were offspring of parents whose fathers were brothers.

From the Departments of Medicine and Psychiatry, Cornell University Medical College, the Russell Sage Institute of Pathology and the New York Hospital.

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2. Vizioli: Dell 'atrofia progressiva nervosa, cited by Marinesco, G.: Contribution à l'étude de l'amyotrophie Charcot-Marie, Arch. de méd. expér. et d'anat. path. **6**:921, 1894.

3. Sainton, P.: L'amyotrophie type Charcot-Marie, Thesis, Paris; G. Steinheil, 1899.

4. Gordon, A.: Remarks on Primary Neuritic Atrophy (Charcot-Marie-Hoffmann Type), with Report of a Case in Which There Was Excessive Indulgence in Tea and Coffee, J. Nerv. & Ment. Dis. **30**:354, 1903.

5. Ballet, G., and Rose, F.: Un cas d'amyotrophie du type Charcot-Marie avec atrophie des deux nerfs optiques, Rev. neurol. **12**:522, 1904.

6. Taylor, J.: Peroneal Atrophy, Proc. Roy. Soc. Med. **6**:50, 1912.

7. Krauss, W.: Atrophia nervi optici und neurotische Muskelatrophie, Ztschr. f. Augenh. **16**:503, 1906.

CASE 1.—*History.*—An unemployed man aged 32 was admitted to the outpatient department of the New York Hospital on Oct. 29, 1940 with the complaint of poor vision and muscular wasting of many years' duration. At the time he first began school the patient noted some impairment of vision. The visual defect increased gradually up to the time of his admission. He stated that objects could not be seen clearly and that he was unable to read ordinary print. Eyeglasses were prescribed on several occasions, but little, if any, improvement in vision was noted when these were worn. About nine years before his admission he first noted nystagmus of both eyes. When he was about 15 years old, the patient noted gradual diminution in the size of both calves, with progressive weakness of the legs. A few years later he began to trip over low objects or uneven places in the floor and sidewalk unless he lifted his feet high while walking. There was no pain or unusual sensation in the extremities.

The muscular wasting and weakness and the difficulty in walking increased steadily, though slowly, over the course of the years up to the time of his admission to the hospital. For about six years the gait had been unsteady, but the patient attributed this to the muscular weakness and impairment of vision.

The past history was noncontributory except for appendectomy for chronic appendicitis at the age of 10 years. He had the usual diseases of childhood and gave no history of any acute illness that could be interpreted as having been an infection of the nervous system. There was no history of syphilis.

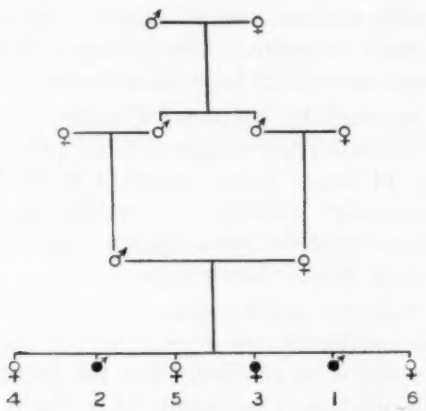

Fig. 1.—Family tree, showing consanguinity of parents. The grandfathers of the patients were brothers. Data on subjects *1, 2, 3* and *4* are given in the case histories. Subject *5* died in infancy, of unknown cause. Subject *6* was without muscular or visual symptoms; she died during childbirth, at the age of 21. Subject *1* has two sons, aged 3½ and 10½ years, respectively, and a daughter, aged 7½ years, who are normal. None of the other subjects has had children.

Examination.—The patient was well developed and well nourished; he walked with a steppage gait on a wide base. There was slight unsteadiness in walking. The pupils were equal and regular and reacted to light and in attempts at near vision. There was lateral nystagmus. Vision was impaired; with the right eye the patient could see the examiner's finger held at a distance of 3 inches (7.6 cm.); vision in the left eye was 17/100. There was definite atrophy of both optic nerves, with marked temporal pallor. A central scotoma, with little peripheral contraction, was considered suggestive of retrobulbar neuritis. There was no facial weakness. The tongue was protruded in the midline without tremor. The muscles of the upper extremities were of normal volume and good power. There were considerable wasting and weakness of all muscles below the knees (fig. 2). The lower third of the thighs showed moderate diminution in volume. There was bilateral foot drop, with shortening of the tendons of achilles. The feet could not be flexed actively by the patient or passively by the examiner even when considerable force was exerted. Extension of the feet was weak. Both feet felt cold to the examiner's hands. All the toes except the great toes were in claw position. The biceps, patellar and achilles reflexes were absent. The triceps reflex was diminished bilaterally. When the soles of the feet were stroked no response was elicited. The superficial abdominal and cremasteric reflexes were active and equal bilaterally. All

four extremities showed sensory defects. Sensibility for light touch was absent over the feet and legs up to a level about 6 inches (15 cm.) below the knees. Perception for pinprick was present in this area but was definitely impaired; this defect was considerable over the toes, moderate over the ankles and relatively slight over the legs. Position sense was absent in the toes. Sensibility for vibration was absent in the feet, legs and knees, but was normal at the level of the hips. Sensibility for pain, light touch and vibration were diminished over both hands, the sensory defects being more evident in the distal portions. Position sense in the fingers was unimpaired. Sensory function was normal in the wrists, forearms and upper portions of the arms.

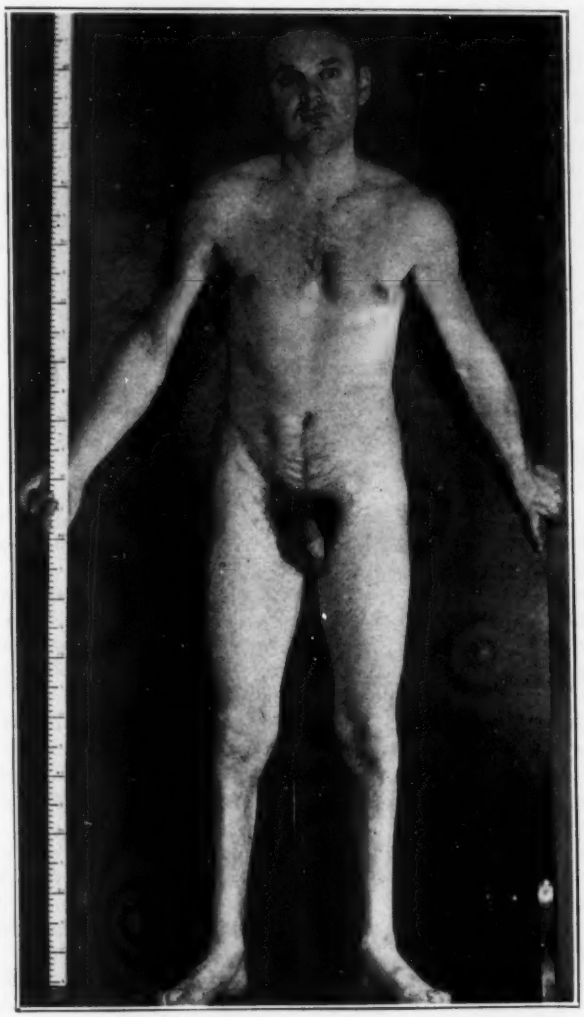

Fig. 2 (case 1).—There is obvious wasting of all muscles below the knees, whereas the muscles of the trunk and upper extremities are well developed. In order to steady himself the patient had to stand on a wide base and support himself with both hands because of the deformity of the feet. This difficulty was less apparent when shoes were worn.

There was no tremor of the extended fingers. Point to point tests were done well except for occasional unsteadiness due to difficulty in seeing the objective. Rapid, alternating rhythmic movements were normal. Romberg's sign was not elicited. Because of deformity of the feet, the patient had difficulty in standing quietly when shoes were not worn. The nerve trunks in the upper portions of the arms and the peroneal nerves were easily palpable and appeared to be moderately enlarged. Pressure over the nerves produced a sensation of tingling in the peripheral portions of the extremities, but sensitivity appeared to be neither reduced nor increased. The Kline reaction of the blood was negative.

The daily urinary excretion of creatinine showed only the slight diminution that was in keeping with the amount of muscular wasting. There was no spontaneous creatinuria, and the creatine tolerance was 95 per cent. The patient weighed 72 Kg.

CASE 2.—I did not examine this patient. The information given here was obtained from members of the family and from two hospitals where he had been a patient in 1935, at the age of 41. He gave a history of weakness and wasting of the legs, deformity of the feet and poor vision since early childhood. Over the course of years the symptoms had increased steadily. At about the age of 31 he noticed wasting of the hands. Examination revealed bilateral far advanced optic nerve atrophy, with severe impairment of vision. Vision in the right eye was 6/200, and that in the left eye was 9/200. There was an internal squint of the left eye. When the eyes were fixed on an object nystagmoid jerks were present. The intrinsic muscles of the hands were wasted, with production of a manus cava deformity. All the muscles of the legs below the knees were wasted, giving the lower extremities a "stork leg" appearance. Both feet showed equinovalgus and cavus deformities. All the tendon reflexes except the biceps and triceps were absent. The abdominal reflexes were active and equal on the two sides. There was diminution in sensibility of the peripheral glove and stocking type for all modalities; vibration and position senses were more affected than were pain, light touch and temperature sensibilities. The peripheral nerves appeared to be enlarged on palpation. Lumbar puncture revealed nothing unusual. The Wassermann reactions of the blood and the spinal fluid were negative.

Subsequent Course.—All the symptoms progressed steadily up to the time of the patient's death, from accidental causes, at the age of 46.

CASE 3.—*History.*—A housewife aged 39 was admitted to the New York Hospital on April 25, 1942 with the complaint of weakness and stiffness of the arms and legs (fig. 3). Six years before this admission she noted gradual onset of stiffness of the back of the legs. A few weeks later she began to complain of increasing weakness and fatigability of the lower extremities. Because of these symptoms and the frequency in micturition which soon developed, she was admitted to another hospital on Aug. 20, 1936, where examination disclosed a spastic-ataxic gait, impairment in performance of tests for equilibrium, a Romberg sign, hyperactive tendon reflexes, a plantar response of extensor type bilaterally, absence of abdominal reflexes, pallor of the temporal half of both optic disks and diminished hearing in the left ear. There was moderate anemia of microcytic type. The concentrations of urea and sugar in the blood were normal. The Wassermann reaction of the blood was negative. Lumbar puncture gave no evidence of spinal block. Examination of the spinal fluid gave the following results: 5 cells per cubic millimeter; a negative reaction for globulin; 24 mg. of protein per hundred cubic centimeters; a colloidal gold curve of 1122100000, and a negative Wassermann reaction. Analysis of the gastric contents gave normal values for free and total hydrochloric acid. Roentgenograms of the skull and spine were normal. The diagnosis was multiple sclerosis. After her discharge from the hospital the patient was treated by parenteral administration of liver extract for five months. After this the symptoms improved, and the patient was almost entirely well for three years.

Two years before her admission to the New York Hospital the patient noted gradual return of her previous disability, first in the right arm and leg and then in all four extremities. Muscular weakness and stiffness increased gradually, although for a time they varied in severity from day to day. At about the same time she noted frequency and urgency in urination and nocturia.

Two and one-half months before her admission to the hospital, muscular weakness and stiffness in all four extremities increased suddenly, and the patient experienced generalized aching sensations in the muscles. The lower extremities became so stiff that the patient was unable to flex them or to lift her feet from the floor. She remained confined to bed up to the time she entered the hospital.

Past Personal History.—The patient had measles, mumps, pertussis, chickenpox and scarlet fever in childhood. In 1928 she had moderately severe influenza. For sixteen years she had had moderate deafness, with occasional tinnitus. The onset of the difficulty in hearing was gradual, and there appeared to be little, if any, progression over the course of many years. Nineteen years before her admission the Wassermann reaction of the blood was positive. There were no clinical manifestations of syphilis. The patient was treated for two years, since which time the Wassermann reactions of the blood and spinal fluid have been persistently negative.

Examination.—The patient appeared to be well nourished. She lay in bed, unable to turn her body or move her legs or right arm. The pupils were equal and regular and reacted

to light and in attempts at near vision. There was an inconstant nystagmus, best seen when the patient looked far to either side; the movements were slow and of equal speed in either direction. Both optic nerve heads appeared slightly white on ophthalmologic examination. No disturbance of speech could be demonstrated. There was no facial weakness. Adventitious movements of the tongue were absent. All four extremities showed moderate reduction in muscular power. There was increased resistance to passive stretch, which was moderate in the right upper extremity, relatively slight in the left upper extremity and considerable in both lower extremities. In performance of point to point tests, both hands showed definite tremor of intention type. Rapid, alternating rhythmic movements were performed poorly by

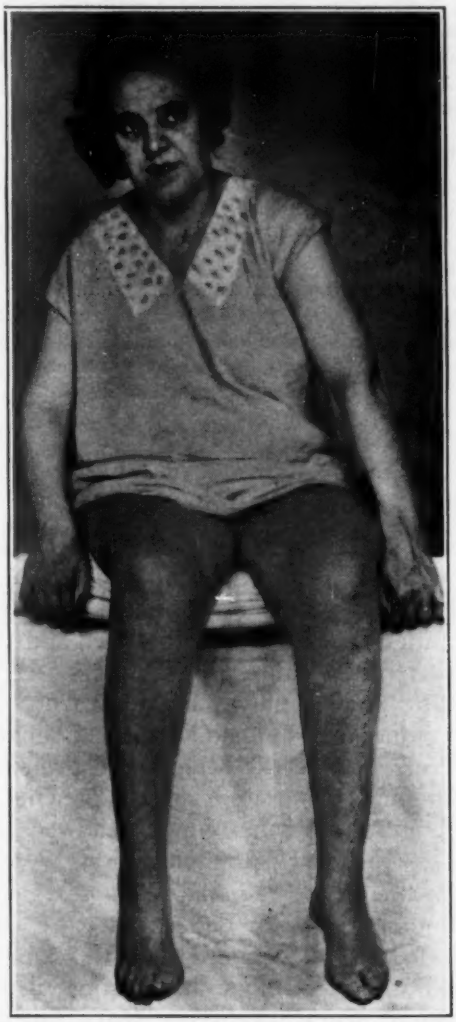

Fig. 3 (case 3).—There is no obvious muscular wasting. The patient was unable to stand because of muscular rigidity and weakness. She could sit steadily for a few minutes when she grasped the edge of the examining table and her back was supported by an attendant (the latter is not shown).

both upper extremities; the right hand could be rotated only slightly and slowly, and movements of the left hand were slow and uncertain. There was slight wasting of the small muscles of the right hand. The biceps and triceps reflexes were increased moderately on the right side and considerably on the left. The patellar and achilles reflexes were extremely overactive on both sides, and there was bilateral ankle clonus. The plantar response was of extensor type bilaterally. The abdominal reflexes were absent on the right side but present on the left. Sensibility for vibration was absent over both feet and tibias and diminished

over both knees and the fingers of both hands. There were no gross defects in sensibility for pain or light touch except for slight diminution below the level of the fourth cervical vertebra. Position sense was reduced in the toes of both feet and in the fingers of the right hand. No fasciculations were observed. Visual acuity was 20/30 in the right eye and 20/40 in the left eye and was not increased by refraction. The otolaryngologic consultant found diminished hearing on both sides, with equal reduction in bone and air conduction. Except for these findings and a soft, blowing systolic murmur, heard over the apex of the heart, and retroversion of the uterus, the results of examination were essentially normal. The blood pressure was 120 mm. systolic and 70 mm. diastolic.

The blood count was as follows: 13.5 Gm. of hemoglobin per hundred cubic centimeters, and 4,000,000 red cells and 9,800 white cells per cubic millimeter, of which 66 per cent were polymorphonuclear leukocytes, 12 per cent band forms, 16 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The Kline reaction of the blood was negative. The levels of calcium and phosphorus in the blood serum were 10.9 and 3.2 mg. per hundred cubic centimeters respectively; the phosphatase level was 2.4 Bodansky units, and the sodium and potassium concentrations were 332 and 17.4 mg per hundred cubic centimeters respectively. The ascorbic acid content of the blood plasma was 0.7 mg. per hundred cubic centimeters. The urine contained a slight trace of albumin but was otherwise normal. The spinal fluid was under normal pressure and contained 6 lymphocytes per cubic millimeter and 30 mg. of protein per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was negative; the colloidal gold curve was 5532100000. Gastric analysis gave normal values for free and combined hydrochloric acid. The basal metabolic rate was — 15 per cent. The electrocardiogram was essentially normal. The average daily urinary excretions of creatine and preformed creatinine, while the patient was maintained on a diet free from these substances, were 0.085 and 0.9 Gm. respectively. The urinary excretion of ascorbic acid was 24 mg. daily. The patient weighed 66.47 Kg.

CASE 4.—A housewife aged 51 was without complaint and considered herself in perfect health. However, there was definite slurring of speech. Otherwise, the examination revealed nothing unusual.

COMMENT

The brothers presented similar symptoms and clinical courses. During childhood both patients had difficulty in walking and vision. At an early age wasting of the feet and calves was observed. Muscular atrophy progressed steadily, until in the lower extremities the part above the knee and that below presented a marked contrast, with the typical picture of "stork legs." The visual disturbance, likewise, increased steadily, and at the time the patients were examined visual acuity was considerably reduced. Ophthalmologic examination showed advanced atrophy of the optic nerves, the process being more pronounced in the temporal halves of the disks. Nystagmus was present in both patients. The tendon reflexes were reduced or absent, and all the extremities showed sensory defects of the "stocking and glove" type. No muscular fasciculations were ever observed.

The cases of these 2 patients were similar in most essential respects to those reported by Vizioli,[2] Sainton,[3] Gordon,[4] Ballet and Rose,[5] Taylor [6] and Krauss.[7] Whether the patient reported on by Reinhard [8] had the same disease is not known. This patient, a man aged 33, had had muscular wasting of peroneal type since the age of 11 years and impaired vision for twenty years, but no examination of the optic nerves was made. A brother of this patient, aged 50, had similar muscular atrophy without visual disturbance. Pain in the lower extremities was prominent among the symptoms complained of by the patients of Vizioli and Gordon but was absent in my patients. The age of onset of disability of all the patients varied considerably; thus, in the patients reported on here the condition began in early childhood; in Vizioli's patients disability began at the ages of 6, 26 and 59; the patient of Ballet and Rose first noted symptoms at the age of 15 years, and in the patients of Gordon and Taylor and Krauss the onset was at the ages of 31, 28 and

8. Reinhard: Beitrag zur Casuistik der neurotischen Muskelatrophie, Deutsche Ztschr. f. Nervenh. **11**:431, 1897.

17 respectively. The age of onset in the patient reported on by Sainton was unknown. In the instances in which the results of neurologic examination were recorded, the tendon reflexes in the lower extremities were much diminished or absent, and sensory defects of "stocking type" were observed. The patient of Krauss had shortening of the achilles tendons, for which a tenotomy had been performed. Muscular involvement in the 2 subjects reported on by Sainton was more prominent in the hands than in the lower extremities. Gordon's patient had definite nystagmus.

All of the 10 patients previously reported on and the 2 patients described in this paper were males. It is of interest that the occurrence of the disease in a female has not been described. In Sainton's patients the disease was transmitted by a normal female, the heredity being similar to that seen in some cases of progressive muscular dystrophy (Milhorat and Wolff [9]). Ten of the 12 patients reported on had atrophy of the optic nerves. The other 2 patients were without visual disturbance but had typical muscular atrophy and were related to patients with both muscular and visual involvement, in 1 instance as a grandson (Sainton [3]) and in the other as a son and brother (Vizioli [2]). In 9 patients the disease was hereditary, but for the remaining 3 patients no history of a similar condition in their families was obtained. In the cases of Vizioli siblings and father and sons were affected; in the cases of Ballet and Rose and those reported here only siblings had the disease; Sainton's cases were those of a grandfather and grandson.

The similarity in the clinical pictures of the 12 patients and the high incidence of heredity make it likely that all the patients had the same clinical condition, which represents either a syndrome quite distinct from the muscular conditions commonly recognized or a definite type of Charcot-Marie muscular atrophy. Dawidenkow,[10] in his discussion of peroneal muscular atrophy, accepted the latter formulation. The absence of visual disturbances in 2 of the patients (Vizioli [2] and Sainton [3]) may possibly support the opinion.

It is difficult to evaluate the relation, if any, between the condition seen in the 2 brothers and that occurring in the sister. The process in the female sibling most likely was disseminated sclerosis. The only feature common to all 3 siblings was atrophy of the optic nerves, most evident in the temporal halves. However, whereas the visual disturbance in the brothers was progressive, and not associated with remissions, the sister's condition improved to the point where vision apparently was entirely normal for a time. Muscular wasting was absent in the sister.

While disseminated sclerosis is the commonest cause of optic neuritis (e. g., Duke-Elder [11]) and the female sibling probably had this disease, the opinion that the condition in the brothers was disseminated sclerosis is not justified. Disseminated sclerosis of familial occurrence has been reported by a few observers, including Kramer,[12] Thums [13] and Wilson.[14] Kramer reported observations on 2

9. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: XII. Heredity of Progressive Muscular Dystrophy; Relationship Between Age at Onset of Symptoms and Clinical Course, Arch. Neurol. & Psychiat. **49**:641 (May) 1943.

10. Dawidenkow, S.: Ueber die neuritische Muskelatrophie Charcot-Marie. Klinisch-genetische Studien: II. Das allgemeine klinische Bild der neuritischen Amyotrophie, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:344, 1927.

11. Duke-Elder, W. S.: Diseases of the Inner Eye, in Text-Book on Ophthalmology: St. Louis, C. V. Mosby Company, 1941, vol. 3, pp. 2097-3470.

12. Kramer: Demonstration aus dem Gebiete der Heredodegeneration, Zentralbl. f. d. ges. Neurol. u. Psychiat. **25**:232, 1921.

13. Thums, K.: Vorläufige Mitteilung über Zwillingsuntersuchungen bei multipler Sklerose, Deutsche Ztschr. f. Nervenh. **139**:34, 1936.

14. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940.

sisters, on 1 of whom necropsy was done, and Thums noted the disease in twins. Wilson twice observed disseminated sclerosis in 2 sisters. However, the clinical findings in my male patients, aside from the optic nerve atrophy, in no way suggested this diagnosis. Muscular wasting is rare in disseminated sclerosis. Taylor [15] reported the case of a man aged 43 with disseminated sclerosis and wasting of the shoulder girdle and upper portions of the arms, but most observers, e. g., Collier,[16] either have never seen wasting of the muscles in this condition, or consider it exceedingly rare (Wilson [14]). The diagnosis of Leber's disease must be considered but is exceedingly unlikely. The onset of Leber's disease usually occurs between the ages of 18 and 23 years, and evidence of structural disease of the nervous system, aside from the involvement of the optic nerves, is so exceptional that Duke-Elder [11] regarded the occurrence of such lesions as incidental. Neuromyelitis optica (of Devic) is as unlikely as are the syndromes illustrated by the cases reported by Peltesohn [17] and Lannois and Lemoine.[18] Peltesohn observed amyotrophic lateral sclerosis associated with bilateral optic nerve atrophy in a man aged 28 years. The patient of Lannois and Lemoine, a woman aged 26, had paraplegia with spastic contractures. She was cachectic and had generalized muscular wasting. At necropsy, sclerosis of the lateral spinal tracts, the bulb and the optic nerves was observed. The nerve trunks in both my male patients appeared to be enlarged on palpation, but not to the degree commonly associated with hypertrophic interstitial neuritis (Dejerine and Sottas,[19] Dejerine and André-Thomas,[20] Long,[21] Hoffmann [22] and Riddoch and Pennybacker [23]). The nerve trunks showed normal sensitivity on pressure. Moreover, the occurrence of optic nerve atrophy in a case of hypertrophic interstitial neuritis seems not to have been observed. There is little to substantiate the opinion stated by Jendrassik [24] that the many and varied hereditary syndromes are merely "forms" of a common inherited defect. This formulation serves no useful purpose in an understanding of these conditions.

On the basis of the data given in this report, it appears justifiable to consider the symptom complex under discussion not as an incidental combination of peroneal muscular atrophy and progressive bilateral optic nerve atrophy but as either a clinical entity or a distinct type of Charcot-Marie muscular atrophy. The significance of the occurrence of disseminated sclerosis with acute optic nerve atrophy in the female sibling can only be conjectural at present.

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23. Riddoch, G., and Pennybacker, J.: Hypertrophic Peripheral Neuritis, Proc. Roy. Soc. Med. **28**:1516, 1935.
24. Jendrassik, E.: Die hereditären Krankheiten, in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol. 2, p. 321.

SUMMARY

The occurrence of progressive peroneal muscular atrophy associated with progressive bilateral optic nerve atrophy in 2 brothers is described. Cases of a similar disease in 8 members of 6 families were reported previously, with 2 other members having typical muscular changes but no visual disturbance. All the patients were males; the occurrence of the syndrome in females appears not to have been observed. A sister of the 2 patients described in this report had bilateral optic nerve atrophy and a disease which most probably was disseminated sclerosis. The relationship, if any, between the condition in the brothers and that in the sister is at present not understood. It appears likely that the syndrome described in this report represents either a clinical entity which is different from the muscular conditions usually recognized or a definite form of progressive peroneal muscular atrophy.

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GENEALOGIC AND CLINICOPATHOLOGIC STUDY OF PICK'S DISEASE

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Knowledge of the clinical and pathoanatomic features of Pick's disease has been considerably advanced in recent years, but the cause and pathogenesis are still incompletely understood. Some of the early investigators (Gans,[1] Reich and Kufs[2]) suggested that the disease may have a hereditary basis, and this assumption has been borne out by subsequent clinical and genealogic studies (Grünthal,[3] Verhaart,[4] Schmitz and Meyer,[5] Haskovec[6] and Löwenberg and others[7]). In 1930 Grünthal[8] made the first pathoanatomic confirmation of this view in a study of 2 brothers, followed by that of von Braunmühl and Leonhard[9] in the cases of 2 sisters (1934). Convincing proof was furnished in 1939 by Sanders and others,[10] who reported on a family showing evidence of the disease in 17 members, the disorder being transmitted through four generations and its presence being confirmed at autopsy in 4 instances. We wish to report on 2 additional families which offer further evidence of the inheritance of this disorder and to outline the manner in which this may be correlated with the clinical and pathoanatomic observations.

FAMILY W

In 1939 Löwenberg and associates[7] reported the case of C. W., which pathoanatomically proved to be one of Pick's disease, the unusual features being the early onset, at the age of 21, and the historical evidence of hereditary transmission.

From the Neuropsychiatric Institute, University Hospital, University of Michigan.

1. Gans, A.: Betrachtungen über Art und Ausbreitung des krankhaften Prozesses in einem Fall von Pickscher Atrophie des Stirnhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **80**:10, 1923.

2. Reich, F.: Zur Pathogenese der circumscripten resp. systemartigen Hirnatrophie, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:803, 1927. Kufs, H.: Beitrag zur Histopathologie der Pickschen umschriebenen Grosshirnrindenatrophie, ibid. **108**:786, 1927.

3. Grünthal, E.: Klinisch-genealogischer Nachweis von Erblichkeit bei Pickscher Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:464, 1931.

4. Verhaart, W. J. C.: Ueber die Picksche Krankheit, Zentralbl. f. d. ges. Neurol. u. Psychiat. **59**:485, 1931.

5. Schmitz, H., and Meyer, A.: Ueber die Picksche Krankheit mit besonderer Berücksichtigung der Erblichkeit, Arch. f. Psychiat. **99**:747, 1933.

6. Haskovec, V.: Pickscher Krankheit, Zentralbl. f. d. ges. Neurol. u. Psychiat. **73**:345, 1934.

7. Löwenberg, K.; Boyd, D. A., and Salon, D. D.: Occurrence of Pick's Disease in Early Adult Years, Arch. Neurol. & Psychiat. **41**:1004 (May) 1939.

8. Grünthal, E.: Ueber ein Brüderpaar mit Pickscher Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:350, 1930.

9. von Braunmühl, A., and Leonhard, K.: Ueber ein Schwesterpaar mit Pickscher Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:209, 1934.

10. Sanders, J.; Schenk, V. W. D., and van Veen, P.: A Family with Pick's Disease. Verhandelingen d. Koninklijke Nederlandsche Akademie van Wetenschappen. Afdeeling Natuurkunde, Sect. 2, D. 38, no. 3, Amsterdam, N. V., Noord-Hollandsche Uitgevers Mij, 1939.

We have since studied a younger brother of this patient and have found that he has the same disease. As illustrated in figure 1, the disease in these 2 brothers (*P 2* and *P 3*) was in all probability inherited from the mother (*H*). At the age of 26 she is said to have shown signs of intellectual decline, which progressed rapidly to complete dementia, the process culminating in death two years after the onset. The rest of the family history showed numerous instances of alcoholism, unstable personality, mental deficiency and psychoses, some of which were apparently organic ("senile dementia"). The case of the younger brother is here reported.

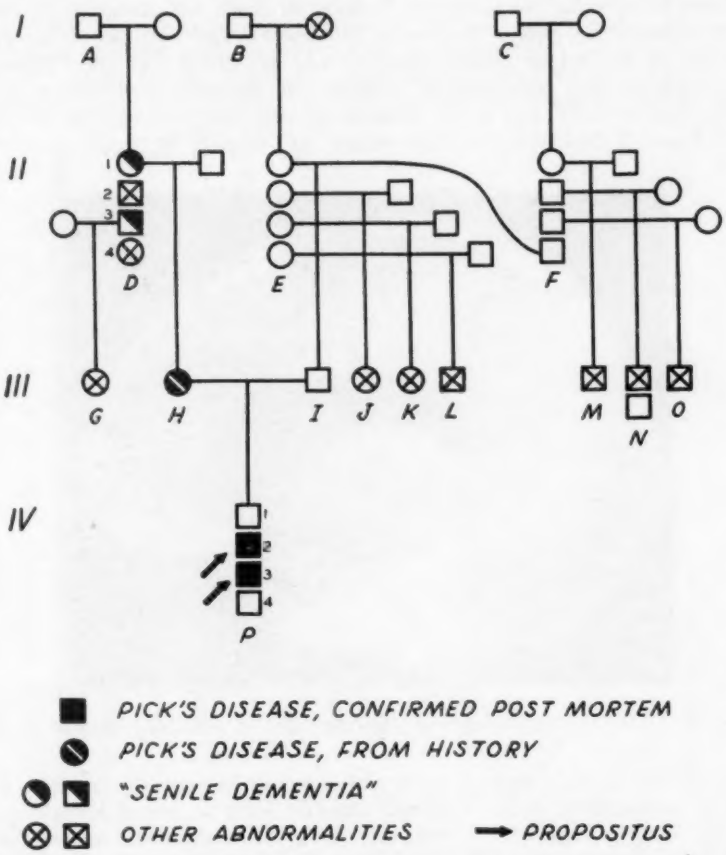


Fig. 1.—Genealogic chart of family W. Generations are indicated by Roman numerals; each sibship is arranged vertically and is identified by a letter, while the various members of each sibship are indicated in the order of age and identified by Arabic numerals—a method introduced by the laboratory of genetics of the University of Michigan.

CASE 1.—*History.*—F. W., a white man aged 25, was admitted to the neuropsychiatric clinic of the University Hospital on Oct. 13, 1938 because, in the opinion of relatives, "he was beginning to show mental symptoms similar to those of his mother and his brother." In the past he had been somewhat unstable, of dull normal intelligence and moderately addicted to alcohol. The onset of his illness was insidious, at about the age of 24, when he became disinterested, mentally dull and at times restless, lost weight, in spite of increased appetite, and showed a lowered tolerance to alcohol. Later he became readily confused when he had to make a decision, and in carrying out errands he seemed to experience more difficulty in understanding than in remembering his task.

General Examination.—The results of physical, neurologic and laboratory studies were normal except for a moderate increase in globulin in the cerebrospinal fluid. A pneumo-

encephalogram disclosed pronounced symmetric dilatation of the lateral ventricles and of the subarachnoid channels, indicating advanced atrophy of the brain (fig. 2). Electroencephalograms were suggestive of organic disease.

Psychiatric Examination.—The patient was superficially cooperative and attentive; he was neat and sociable, but passive, and was distinctly lacking in initiative in that he did not engage spontaneously in conversation or in ward activities. He responded to questions briefly, though relevantly. He readily became confused by new and unfamiliar situations. He was usually apathetic but was subject to unmotivated irritability. There were no psychotic manifestations.

Psychologic tests, although frequently producing variable and unpredictable results, nevertheless indicated a specific type of impairment. While he was correctly oriented for time, place and person, there was spatial and temporal disorientation in the sense of Goldstein.[11] He was confused with regard to direction, location in space and duration of time and failed with the more abstract geometric designs of Goldstein's special test. Memory for remote and recent events as applied to factual material was preserved, but the "capacity of voluntary memory," such as that employed in outlining the sequence and relation of events, was defective. Retentive memory was fairly well preserved, and although he could repeat only 6 digits forward and 3 backward, he experienced no difficulty in recall of word pairs, sentences and stories. In reproduction of stories his account became sketchy and confused only when he failed to comprehend them. Learned material, such as school knowledge, and ability to calculate were largely retained. There was no gross impairment of perception, but the more complex tests, such as the Ebbinghaus and the Kent-Rosanoff, revealed defects. On the Stanford-Binet scale he earned a mental age of 10 years and 10 months and an intelligence quotient of 72, his successes being scattered over a range of 9 years and 4 months. Failures were demonstrated at the lowest age levels in the Minkus completion tests, in the sensing of absurdities, in the reproduction of designs and in free associations, while failures in memory occurred only at higher age levels. Because of particular difficulty with form perception, on the Grace Arthur performance scale his intelligence quotient was only 44. There was no evidence at this time of aphasia or apraxia. The Rorschach test (fig. 3) elicited 7 out of 10 of the Piotrowski signs of organic deterioration and showed a reversed color score, suggesting a "cortical degenerative process."

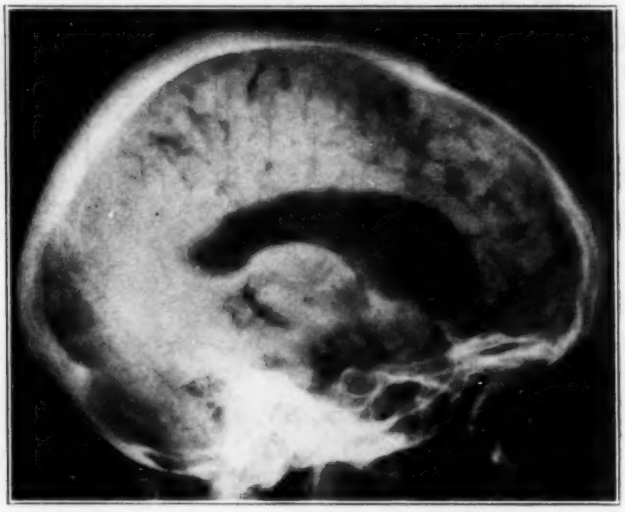


Fig. 2 (case 1).—Lateral encephalogram, showing signs of advanced atrophy of the cortex.

Course of Illness.—After the patient's discharge from the hospital his condition showed a rapid decline, so that when he was readmitted a year later he was already in an advanced stage of his illness. At this time neurologic examination elicited parkinsonian features, characterized by a festinating gait, loss of associated movements and generalized rigidity

11. Goldstein, K., and Katz, S. E.: The Psychopathology of Pick's Disease, Arch. Neurol. & Psychiat. **38**:473 (Sept.) 1937.

with the cogwheel phenomenon, which was more noticeable on the right side. There were adversive phenomena in the form of grasp and *Atz* (sucking) reflexes. He was incontinent of urine and feces and entirely helpless in his personal care. He was now completely passive, mute, entirely without initiative and inattentive but euphoric. His responses were fragmentary, "automatic" and evasive and showed a tendency to perseveration and echolalia. He seemed to be grossly disoriented and deteriorated; yet on vigorous stimulation preserved remnants of memory could be elicited, such as, on occasion, a surprising return of 6 digits forward. Formal psychologic tests were no longer possible. At this time there was definite evidence of aphasia, apraxia and agnosia, although the degree of these defects could not be properly evaluated because of the deterioration. The disturbance in speech consisted of reduction in expression amounting to mutism, of impairment of reception and of naming defect, but there were no signs of complete breakdown, such as jargon or paraphasia. The apraxia was of ideational type, with complete loss of knowledge of skilled acts, such as writing, drawing and obeying of simple commands, although involuntary and imitative movements were possible. There also seemed to be impairment in the recognition of objects. The patient was transferred to Ypsilanti State Hospital.[12] As the disease advanced he began to manifest motor disturbances characterized by persistent rhythmic tremor of the

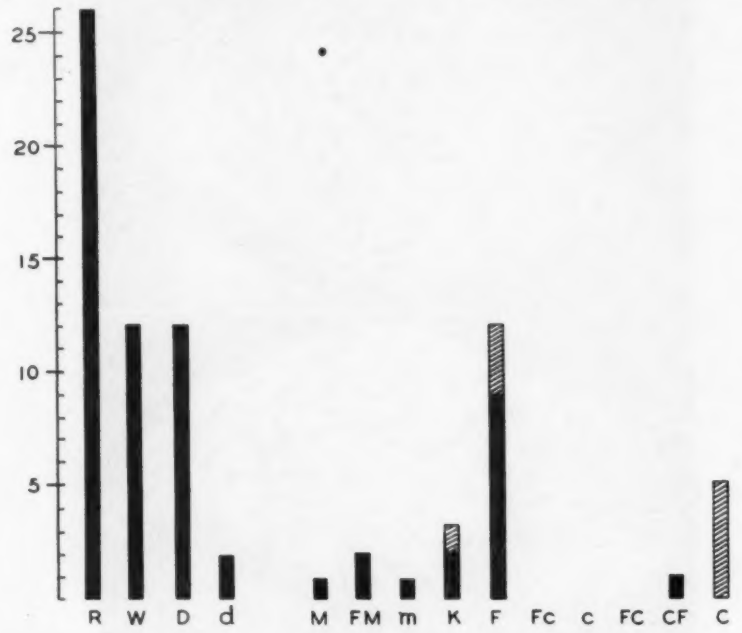


Fig. 3 (case 1).—Rorschach psychogram.

right upper extremity, generalized myotatic irritability and myoclonic contractions on passive motion, hyperreflexia, some ataxia and a slow, shuffling gait with a list to the right; all signs were more pronounced on the right side. Toward the end of his life there was complete rigidity of all the extremities, and the skin was greasy and covered with a red maculopapular rash. After an elevation of temperature, of central origin, to 105 F. the patient died, the duration of the disease being approximately two and one-half years.

Autopsy.—Examination of the internal organs showed nothing significant. The brain weighed 1,145 Gm. The leptomeninges were moderately thickened; all the visible vessels were delicate. The cerebral hemispheres were slightly asymmetric, the left being smaller than the right. Atrophy of the "knife blade" type was present in symmetric areas of the frontal, temporal and parietal lobes of the two hemispheres, alternating with well preserved intervening regions (fig. 4 *A*). In the frontal lobe there was equally severe atrophy of all

12. Dr. O. R. Yoder, superintendent, and Dr. P. N. Brown, clinical director, of the Ypsilanti State Hospital, and Dr. P. V. Wagley, former superintendent of Pontiac State Hospital, cooperated in furnishing the material presented in this paper.

gyri on the basal, lateral and medial surfaces, including the entire cingulate gyrus. In the rolandic region the atrophy on the right side stopped abruptly at the precentral sulcus, sparing the precentral gyrus, but on the left the gyrus was also affected, especially in its midportion. The postcentral and paracentral convolutions were well preserved bilaterally. In the parietal region there was severe atrophy bilaterally of the supramarginal and angular gyri, of the greater part of the superior parietal gyrus and of the entire precuneus. The occipital lobe was well preserved. The temporal lobe was severely atrophic, except for the posterior two thirds of the superior temporal gyrus, which appeared intact, and moderate involvement of the hippocampus. Sagittal sections demonstrated in addition severe atrophy of the insula bilaterally, while the transverse gyri of Heschl were well preserved. The cortex and white matter of the affected convolutions were poorly demarcated, yellowish gray and of leathery consistency. There was atrophy of the corpus callosum except for the splenium. The lateral ventricles were greatly dilated throughout. The caudate bodies

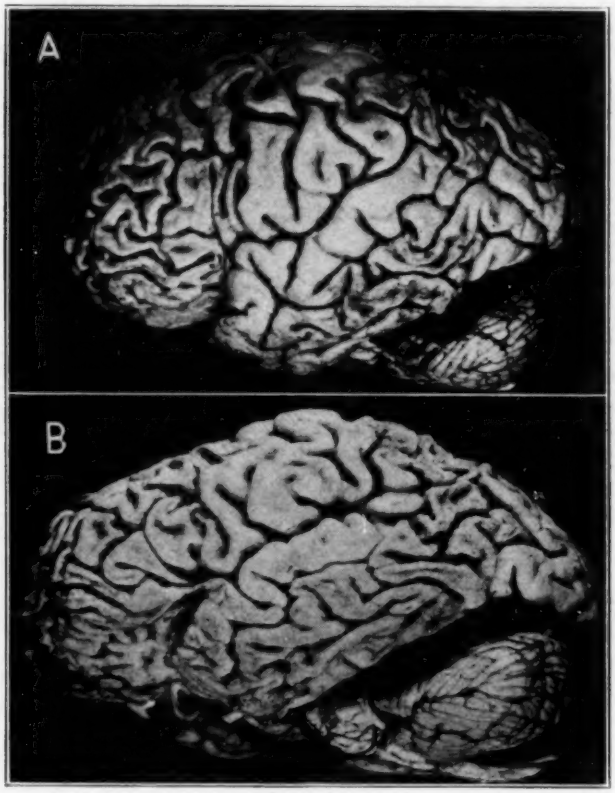


Fig. 4.—Lateral aspect of the brain, showing atrophy of the frontotemporoparietal type. *A*, the brain of the patient in case 1, and *B*, that of his brother.

appeared flattened and atrophic; the remaining basal ganglia, the brain stem and the cerebellum were grossly normal.

Microscopic Observations.—Histologically the changes in the cerebral cortex were more widespread than was indicated grossly, being present to varying extent also in nonatrophic areas. For purposes to be discussed later, their exact distribution was mapped out in accordance with the cytoarchitectonic charts of Brodmann. The changes were classified according to the degree of severity, as follows:

1. Severe (fig. 5 *A*): The severe changes were restricted to the macroscopically atrophic convolutions. Here the cortex was reduced to less than half its normal width, the cytoarchitectural and myeloarchitectural patterns being largely destroyed. The majority of neurons had fallen out and were replaced by glia, the remaining nerve cells being either shrunken, shadow forms or, more commonly, inflated elements, some of which contained argentophil inclusion bodies. In the granular cortex the pattern of degeneration was of

the laminar type; layers III, V, II and VI were destroyed in that order, frequently only lamina IV being left intact. In the agranular cortex the disturbance of the cytoarchitecture was more diffuse. The changes tended to be more severe in the troughs than in the crests of the convolutions. The inflated elements were more common in the deeper layers and in the relatively less advanced areas of degeneration. The glial reaction was outspoken, being largely composed of macroglia, which gave rise to dense marginal and subcortical gliosis, while the intervening cortex contained numerous well developed astrocytes.

2. Moderate (fig. 5 *B*): These changes occurred in areas in which there was no appreciable atrophy. Here there were diffuse rarefaction, especially of lamina III, and scattered degenerated neurons, particularly of the inflated variety.

3. Mild (fig. 5 *C*): These changes were observed in areas which were grossly well preserved, the cytoarchitecture was intact, but scattered shrunken neurons and occasional inflated elements were present; frequently the alterations were so minimal that the cortex appeared practically normal. Nowhere in the gray matter was there any evidence of vascular change, proliferation of gitter cells, deposition of fat or increase in iron. Senile plaques and Alzheimer neurofibrillar alterations were absent.

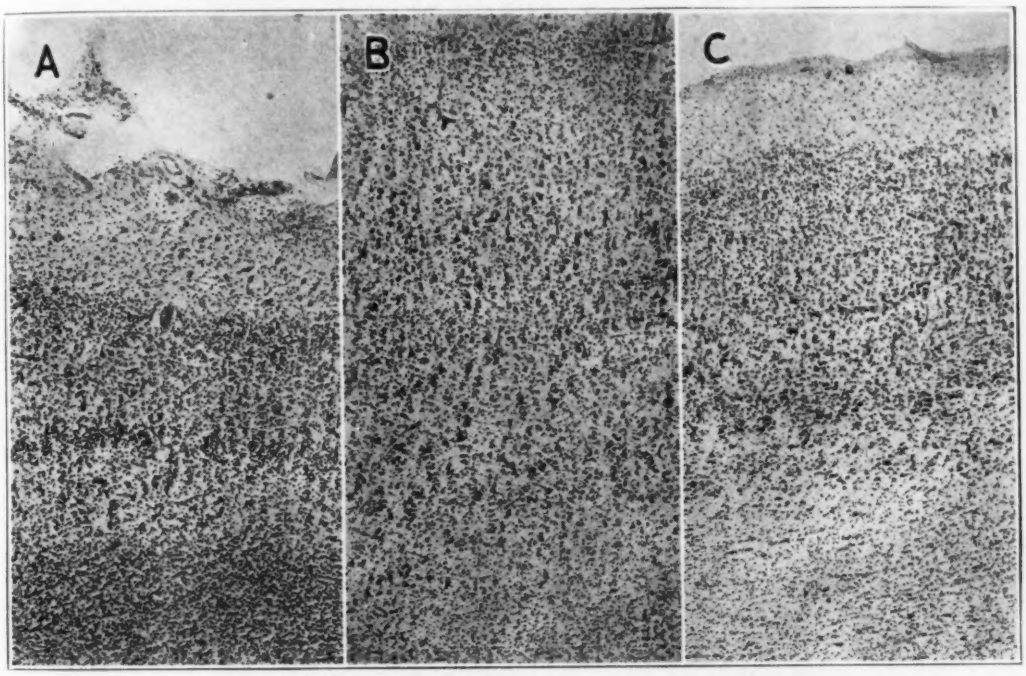


Fig. 5 (case 1).—*A*, severe degeneration of the parietal cortex; *B*, moderate rarefaction in the preparietal region, and *C*, mild changes in the postcentral area. Nissl stain; Zeiss planar lens no. 20.

In the white matter of the atrophic convolutions there were demyelination, dense gliosis and, in some areas, unusual activity in the form of accumulations of fat-laden gitter cells. The corpus callosum was severely demyelinated except for the caudal part of the splenium; there was moderate demyelination of the anterior commissure and, to a milder degree, of Arnold's and Türck's bundles. The claustrum, the nucleus amygdalae and the caudate body contained fairly numerous inflated cells, although there was no appreciable loss of parenchyma, the atrophy of the caudate nucleus, which was due to compression by the enlarged ventricles, being more apparent than real. The putamen and the globus pallidus appeared normal. In the thalamus there were focal areas of secondary degeneration, chiefly in the anterior and medial nuclei. The substantia nigra showed nonspecific degeneration, with remnants of pigment in phagocytes; there were proliferation of glia cells in the red nucleus and an occasional inflated cell in the hypothalamus and in the central gray matter of the aqueduct. There were no microscopic changes in the cerebellum, pons, medulla or cervical portion of the cord.

FAMILY D-G

In this family group, the hereditary features shown in the accompanying chart (fig. 6) are so evident as to permit a detailed genealogic analysis. The cases of the 2 propositi (*G 1* and *I 7*), the diagnosis of whose condition as Pick's disease was established pathoanatomically, will be discussed first.

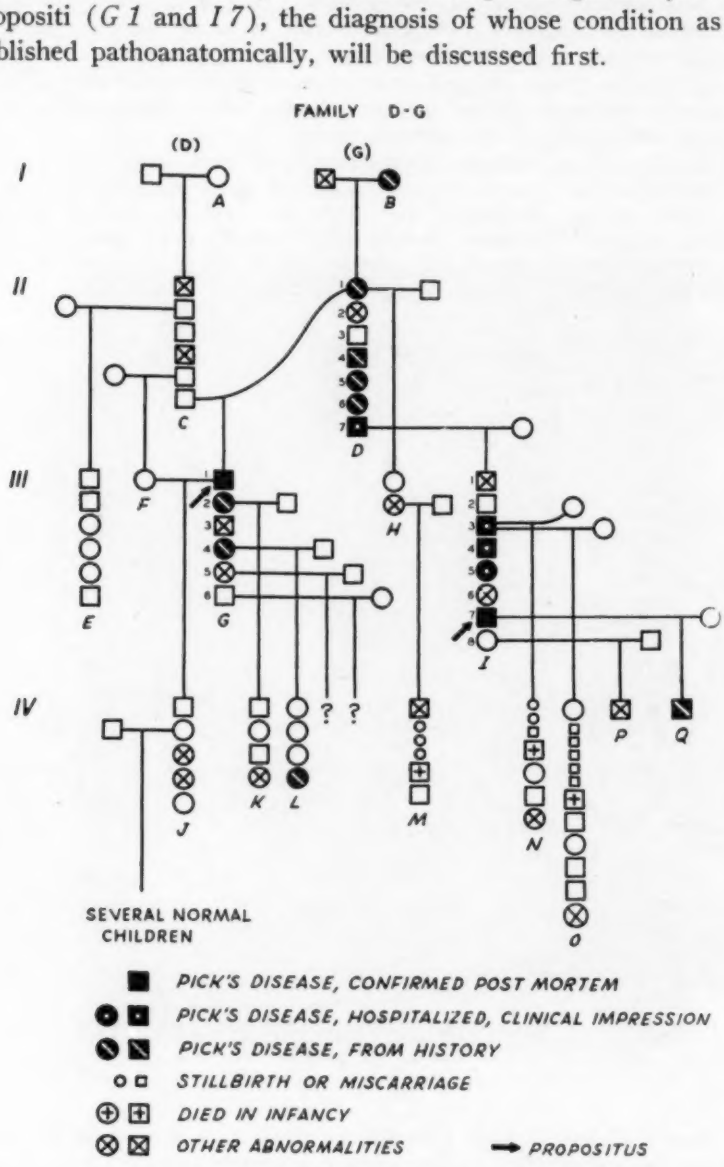


Fig. 6.—Genealogic chart of family D-G.

CASE 2.—G. D. (*G 1*), a white man aged 64, was admitted to Pontiac State Hospital with signs of mental deterioration. The patient had always been of extremely unstable, egocentric and sadistic personality, socially maladjusted and, in his youth, heavily alcoholic. With advancing age these personality traits became more prominent, gradually merging with the symptoms of his illness, which became apparent about three years prior to hospitalization. At that time he began to show increasing signs of mental confusion and dulling of comprehension, such as inability to play cards or to perform simple tasks. Later he became careless in his personal habits, untidy and incontinent, had a staggering gait and was finally completely helpless. In the hospital he was in a stage of advanced deterioration; he was apathetic and inattentive; speech was reduced, and judgment, memory and

orientation were grossly impaired. The results of physical, neurologic and laboratory examinations were essentially without significance. He died about six weeks after admission to the hospital.

Autopsy.—Examination of the internal organs showed only moderate generalized arteriosclerosis. The brain weighed 1,175 Gm. The leptomeninges were moderately thickened; the basal vessels showed patchy sclerosis. The cerebral hemispheres were of equal size and revealed bilaterally symmetric and circumscribed atrophy, restricted to the frontal lobes (fig. 7*A*). In the frontal region all the convolutions were distinctly atrophic, with relatively greater involvement of their superior and parasagittal parts, the atrophy terminating at the precentral and cingulate sulci. Section revealed also atrophy of the gyri breves of the insula and of the anterior third of the corpus callosum. The lateral ventricles were dilated, but the basal ganglia, brain stem and cerebellum appeared normal.

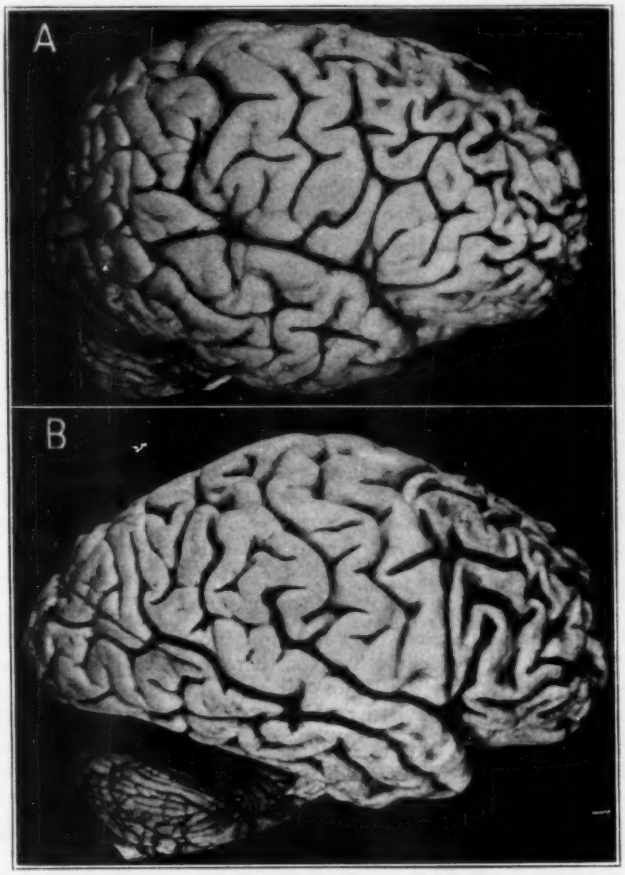


Fig. 7.—Lateral aspect of the brain, showing (*A*) atrophy of the frontal type (case 2) and (*B*) atrophy of the frontotemporal type (case 3).

Microscopic Observations.—As in case 1, the changes in the cortex were classified as severe, moderate and mild, the distribution of the lesions being outlined later. The histologic picture was essentially similar to that in case 1 but showed the following additional features: The degeneration was less intense, being largely restricted to supragranular layers II and III; when severe, it showed a distinct spongy state; the better preserved deep layers contained scattered inflated elements with occasional argentophil inclusion bodies; the reaction in the gray matter was predominantly macroglial, and there was dense gliosis in the white matter, but no signs of lipid deposits or proliferation of blood vessels; in the subcortical areas there was only an occasional inflated cell in the corpus striatum, and the neurons of the substantia nigra were moderately reduced.

Case 3.—E. G. (*I 7*), a white man aged 62, was admitted to Ypsilanti State Hospital in a state of severe mental confusion. He had always been known in the community as a chronic

alcohol addict, and as socially maladjusted, but no information was available regarding the onset of his illness. About a year prior to hospitalization he was placed in a county infirmary, at which time he was already extremely confused and resistant, with complete loss of a sense of propriety, and his condition was regarded as "senile dementia." From that institution he was admitted to the hospital in a condition of extreme physical decline, due to cardiac decompensation. Mentally, he was completely out of touch with his surroundings, unresponsive, antagonistic, incontinent and entirely helpless. He died five weeks later, of bronchopneumonia.

Autopsy.—Examination of the internal organs revealed advanced generalized arteriosclerosis, particularly of the heart and kidneys, and "alcoholic" cirrhosis of the liver. The brain weighed 1,125 Gm. The leptomeninges were moderately thickened; the basal vessels were delicate. The cerebral hemispheres were slightly asymmetric, the right being smaller than the left. Symmetric, circumscribed areas of "knife blade" atrophy were present in the frontal and temporal lobes of the two hemispheres (fig. 7 *B*). In the frontal lobe the atrophy involved equally all gyri on the basal, lateral and medial surfaces, stopping abruptly at the precentral sulcus, while tapering off gradually at the paracentral lobule and the part of the cingulate gyrus below it. All gyri of the temporal lobe were severely atrophic except for the preserved posterior half of the superior temporal gyrus, including Heschl's convolutions, and the hippocampus. A small central area of the supramarginal gyrus was the only atrophic part of the parietal lobe, while the occipital lobe was entirely preserved. Sagittal sections showed, in addition, severe atrophy of the entire insula and of the corpus callosum, with the exception of the splenium, and moderate involvement of the caudate body. The lateral ventricles were greatly dilated. The brain stem and the cerebellum were grossly normal.

Microscopic Observations.—As in the previous cases, the changes in the cortex were of severe, moderate and mild degrees. While the histologic picture was similar to that in the preceding cases, certain minor differences were noted. The degeneration of the cytoarchitectural pattern was more diffuse than laminar in type, although layers III and V were preferred. A spongy state of the tissue was common. Inflated neurons were numerous, with occasional argentophil inclusion bodies. The white matter of the atrophic gyri exhibited gliosis and a lacunar state, due to dilatation of perivascular spaces. There were neither accumulations of lipids nor changes in the blood vessels. The amygdaloid nucleus contained occasional inflated cells. The caudate body presented compression of the tissue and scattered Alzheimer glia cells of type II, a change usually encountered in association with cirrhosis of the liver. In the dorsal thalamus there were foci of secondary degeneration. The subthalamic body contained occasional inflated elements. The cerebellum showed scattered loss of Purkinje cells. There was moderate secondary degeneration of the anterior commissure, but none of the long projection tracts.

OTHER MEMBERS OF FAMILY D-G

The chart shows that family G was the carrier of the disease, transmitting it by marriage to family D. In addition to the preceding 2 cases, there were 13 instances in which the disease was suspected, either on the basis of the history or from the clinical impression on hospitalization. These cases are described in the order of the generations in which they occurred.

GENERATION *I.*—The first known affected member was *B*, the maternal grandmother of *G 1* (case 2); she was described as having become in her advanced years "insane, confused and likely to wander about," and she may have been in a hospital for mental disease.

GENERATION *II.*—In sibship *D*, consisting of the 7 children of patient *B*, 5 members were apparently afflicted with the disease. *D 1*, the mother of *G 1* (case 2), at the age of 65 showed symptoms characterized by "increasing incompetence in the management of her home, inability to recognize familiar surroundings, lack of understanding of adult conversation, childish behavior and peculiar speech," progressing to complete dementia and terminating in death, at the age of 75. *D 4*, *D 5* and *D 6* showed "similar symptoms" of progressive mental deterioration. *D 7*, a chronic alcohol addict, was admitted to a hospital for mental disease at the age of 68 in a terminal state of advanced deterioration. His condition was diagnosed as "senile arteriosclerotic psychosis."

GENERATION *III.*—Sibship *G* consisted of the children of *D 1*. Of these 6 siblings, 3 were afflicted: *G 1*, the patient in case 2; *G 2*, who had a severe psychopathic personality with beginning of mental symptoms at the age of 52, and died two years later in a mental disease hospital; *G 4*, who likewise had a psychopathic personality and who later, according to the statements of relatives, manifested a mental illness "similar to that of her mother."

Sibship *I* consisted of the children of *D 7*. Of the 8 siblings, 4 apparently had the disease. *I 3* was a chronic alcohol addict, of unstable personality, who at the age of 55 began to show "increasing incompetence, loss of social and moral sense and progressive intellectual impairment"; his condition was diagnosed in a hospital for mental disease as "presenile dementia";

death occurred at the age of 64. *I 4* had "a similar illness at the age of 55, characterized by initial symptoms of loss of moral sense and paranoid attitude," followed by progressive mental deterioration; he died at the age of 57 in a mental disease hospital. *I 5* manifested symptoms at the age of 52, with features of restlessness, odd behavior and intellectual decline, progressing to complete mutism and dementia; her condition was diagnosed in a mental disease hospital as "psychosis with cerebral arteriosclerosis"; death occurred at the age of 57. *I 7* is the patient described in case 3.

GENERATION *IV*.—In the opinion of relatives, *L 4*, the daughter of *G 4*, and *Q*, the only son of *I 7* (case 3), are already showing the initial symptoms of the disorder, but this has not been clinically verified.

It will be noted that in both sibships *G* and *I* there was one pathoanatomically verified case of Pick's disease. This and the striking similarity of the age incidences and the clinical courses of the affected members make it probable that they all suffered from the disease. In addition, the chart shows other psychiatric abnormalities in this pedigree, such as several instances of psychopathic personality, chronic alcoholism, feeblemindedness, convulsive disorders, various affective psychoses and psychoneuroses.

COMMENT

Hereditary Considerations.[13]—Pick's disease, as exemplified in the two families described here, shows a definitely dominant pattern of inheritance. Thus, in both families, after the defect once made its appearance, it was regularly inherited by some of the offspring of an affected parent, and not by the offspring of two normal parents. In the pedigree of family W, the first presumptive appearance of the defect was in one member of a large sibship, only the defective sib being indicated on the chart. This appearance of the disease may be explained as a new mutation unless it can be proved that the defect was already present in some of the antecedents (persons with "senile dementia"). Of the 4 offspring of this originally affected person, the defect appears in 2, which is the usual mendelian ratio of 1 : 1 for a dominant trait. In the pedigree of family D-G, the heterozygotic defect appeared in 12 of the 25 offspring of an affected parent who had reached the age at which the disease might be expected to develop. The fourth generation of this family is too young to determine whether any are afflicted, although 2 members show possible incipient signs of the disease; their ages are unknown. A dominant inheritance of the disease has also been assumed by Sanders and associates[10] in their family.

It is of special interest to note that the age of onset of the disease differed greatly between the two families but was fairly constant within each. In family W the age of onset was at about the middle of the third decade, while in family D-G it was between the ages of 50 and 65 and showed a tendency toward an earlier onset in successive generations. This phenomenon is also confirmed in the literature and is commonly observed with other hereditary disorders.

There does not appear to be any significant sex linkage. Although the total number of females affected in family D-G was considerably greater than the number of males, a glance at each sibship will show some in which more females and others in which more males were affected, while 3 affected sibships consisted only of females. This observation is also confirmed by the literature.

Since so-called sporadic cases of Pick's disease are frequent, the opinion has been advanced that while in some cases the condition is hereditary, in others it may have a nonhereditary cause (Schmitz and Meyer,[5] Sanders and associates[10]). However, cases appearing to be sporadic may not be truly so, since members of the kindred other than those obviously affected, even in a family with a dominant

13. The staff of the laboratory of genetics of the University of Michigan assisted in the analysis of the genealogic data.

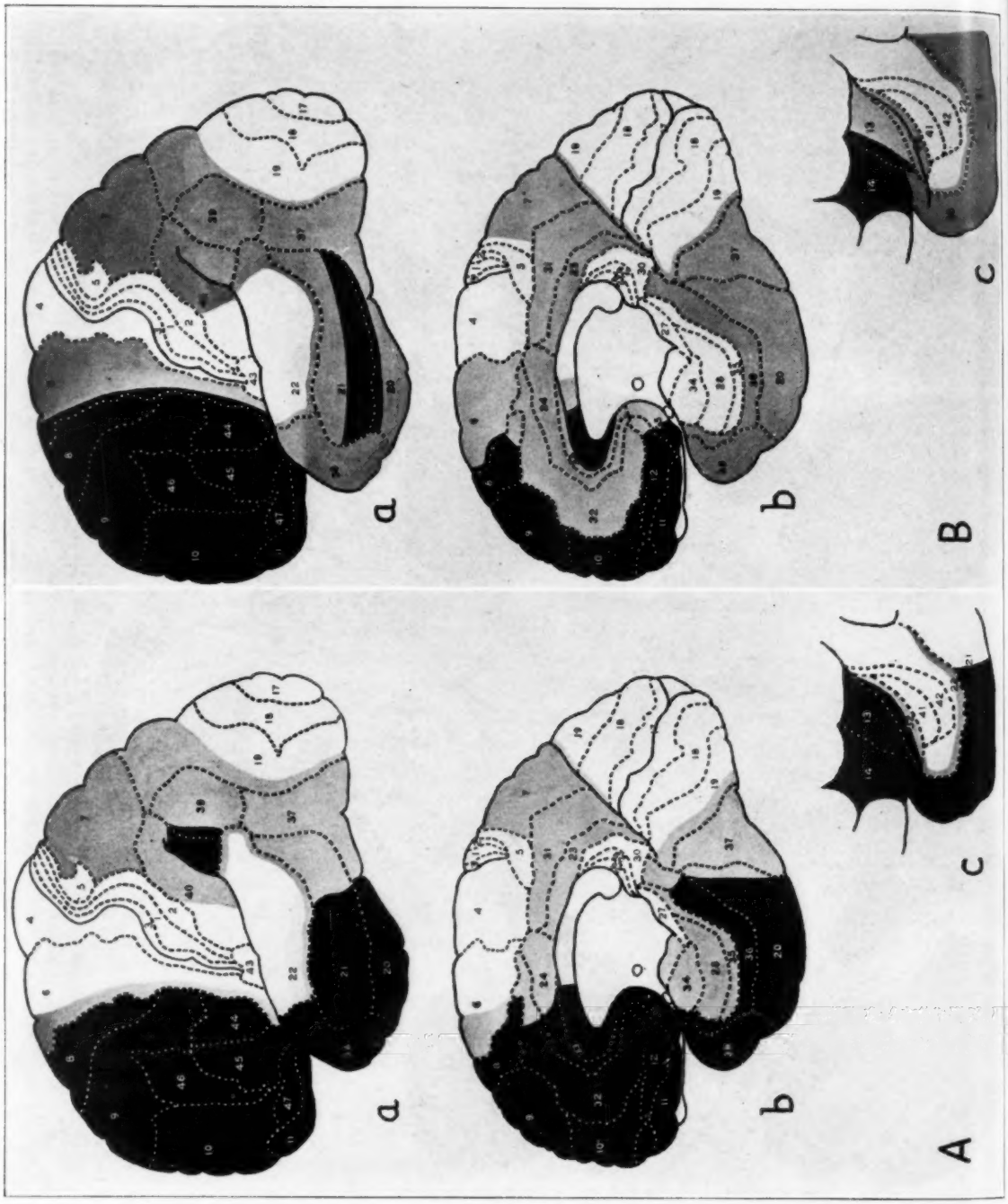
type of inheritance, may have the disease unknown to the investigator. Also, in some sporadic cases the disease may be hereditary, but of the recessive type; in such a situation both parents would appear normal, and conceivably there might be no affected sibs. Lastly, it does not appear possible that an exogenous factor could produce a pathoanatomic effect exactly like that produced by an endogenous factor of hereditary type.

In addition to the specific hereditary factor, Pick's disease is often associated with a general familial stigmatization by other degenerative and constitutional mental disorders. This has been emphasized by Löwenberg and associates,[7] Haskovec[6] and others, and was especially pronounced in family D-G.

Clinical Considerations.—Cases of Pick's disease are rarely suitable for adequate clinical investigation, since they are usually first discovered when the disorder is in an advanced stage. Case 1, however, afforded us the rare opportunity of studying the condition from its initial stage. At this time the vague clinical signs of mild mental dulling and reduced initiative seemingly failed to explain the surprisingly advanced atrophy of the cortex, as revealed by a pneumoencephalogram. However, with the aid of psychologic methods of investigation, as devised by Goldstein, it was possible to demonstrate that the fundamental disturbance consisted of impairment in "categoric" thinking. This revealed itself in defects of abstract behavior toward spatial and temporal orientation, perception and association, in impaired capacity for voluntary memory and in inability to select between several possibilities in a situation, while learned and concrete material was largely retained. As the disease advanced, this type of deterioration in thinking resulted in complete paralysis of speech and action, bewilderment, perseveration and stereotypy, so that the distinction between abstract and concrete behavior was no longer demonstrable. To this state were now added signs of aphasia, apraxia and agnosia, characterized by disturbance in the "higher" qualities of the functions concerned, but without complete dissolution of language and with preservation of involuntary movements. Toward the end the picture was dominated by neurologic features of parkinsonian-like anomalies in posture and tone, adversive phenomena of sucking and grasping reflexes, myoclonic contractions and tremors and vegetative signs of seborrhea, with death from central hyperthermia. Such a clinical course seems to indicate a system disorder in which the higher functions of the cortex are exclusively or predominantly affected. This fundamental principle would seem to apply to all cases of the disease, even though the individual symptoms might differ. These differences may depend on such factors as anatomic localization, duration and tempo of the process and previous personality structure. Thus, clinically, the patient's condition in case 1 resembled closely that of his brother, as reported by Löwenberg and associates,[7] both representing the frontotemporoparietal type of atrophy (fig. 4 *A* and *B*). The symptoms in case 2, suggesting the "frontal lobe syndrome," correlated well with the predominance of the atrophy in the frontal region. The tempo of the disease varied widely, from the relatively rapid course of two and a half years in case 1 to the slowly progressive course of ten or more years in some cases in family D-G. In addition, the severe psychopathic trend in family D-G distinctly colored the clinical pictures.

Pathoanatomic Considerations.—That the pathoanatomic features indicate a system disease is affirmed by some authors and denied by others. On comparing the distribution of the changes with the cytoarchitectonic fields of Brodmann and with ontogenetic and phylogenetic charts, Gans[1] concluded that the disease was a system disorder strictly affecting the genetically youngest fields of the brain.

Fig. 8.—Distribution of the changes in the cytoarchitectural fields of Brodmann (*A*) of the patient in case 1 and (*B*) of his brother. In both *A* and *B* of this figure, and in figure 9, *a* indicates the lateral surface; *b*, the medial surface, and *c*, the insular and the sylvian surface of the temporal lobe. Black areas denote severe changes; gray areas, moderate changes, and white areas, mild changes in the cytoarchitectural fields. Numerals indicate the cytoarchitectural fields of Brodmann.


A
B
a
b
c
a
b
c

Onari and Spatz [14] expressed the belief that, although the process has its center in genetically young regions, there is no strict conformity, while Sanders and associates rejected the idea of a system disease.

In this contribution a similar attempt has been made to outline the distribution of the changes of the cortex in our cases in accordance with Brodmann's cytoarchitectonic fields (figs. 8 and 9). To arrive at a fairly accurate estimate, the different fields were examined in Nissl preparations of complete serial sagittal or horizontal sections. In the accompanying table, a comparative analysis is

Comparative Analysis of Degrees of Involvement of Various Cytoarchitectonic Fields in Four Cases of Pick's Disease

Major Regions	Cytoarchitectonic Fields of Brodmann	Case 1	Brother of Patient in Case 1	Case 3	Case 2
Frontal.....	8; 9; 10; 11; 44; 45; 46; 47	Severe	Severe	Severe	Severe
Precentral...	6	Severe	Severe (rostral) to moderate (caudal)	Mild	Moderate
	4.....	Moderate (except for severe change in midpart of left side)	Mild	Mild	Mild
Insular.....	14; 13; 52.....	Severe	Severe	Severe	Severe (rostral) to moderate (caudal)
Temporal....	22; 41; 42, or supratemporal.....	Mild	Mild	Mild	Mild
	36; 37; 38; 20; 21.....	Severe	Severe	Severe	Severe (center of fields 20 and 21); moderate otherwise
Hippocampal	35; 28; 34.....	Severe to moderate	Moderate to mild	Moderate	Mild
	27, or presubiculum, and cornu ammonis.....	Mild	Mild	Mild	Mild
Postcentral..	3; 1.....	Mild	Mild	Mild	Mild
	2; 43.....	Moderate	Moderate	Mild	Mild
Parietal.....	5, or preparietal.....	Moderate	Moderate	Mild	Mild
	7; 40; 39.....	Severe	Severe	Severe (center of field 40) to moderate elsewhere	Moderate
Occipital.....	17; 18; 19.....	Mild	Mild	Mild	Mild
Cingulate....	25; 33; 24; 32; 23; 31.....	Severe	Severe	Severe (rostral) to moderate (caudal)	Moderate
Retrosplenial	26; 29; 30.....	Mild	Mild	Mild	Mild

made of the degree of involvement of the various cytoarchitectonic fields, permitting the following conclusions:

1. The major regions which are regularly affected are: the entire frontal area; the temporal, with the exception of the supratemporal, and the parietal, with the exception of the preparietal. These regions are not all equally involved in any given case, as is evident from the various combinations of macroscopic atrophy. However, the "susceptibility" of all these regions is shown by an analysis of our cases. In case 1 and in that of the patient's brother all three regions were severely involved; in case 3, in which the gross atrophy was of the frontotemporal type, there was already a small central area of atrophy in field 40 of the parietal region;

14. Onari, K., and Spatz, H.: Anatomische Beiträge zur Lehre von der Pickschen umschriebenen Grosshirnrinden-Atrophie, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:470, 1926.

in case 2, in which grossly the atrophy was of the frontal type, there was beginning atrophy in adjacent fields 20 and 21 of the temporal region. Such observations justify the assumption of "primary foci of atrophy" (Grünthal [8]). The atrophy of the anterior and the posterior part of the insular region seems to depend on the involvement of the frontal and the temporal region respectively, while the

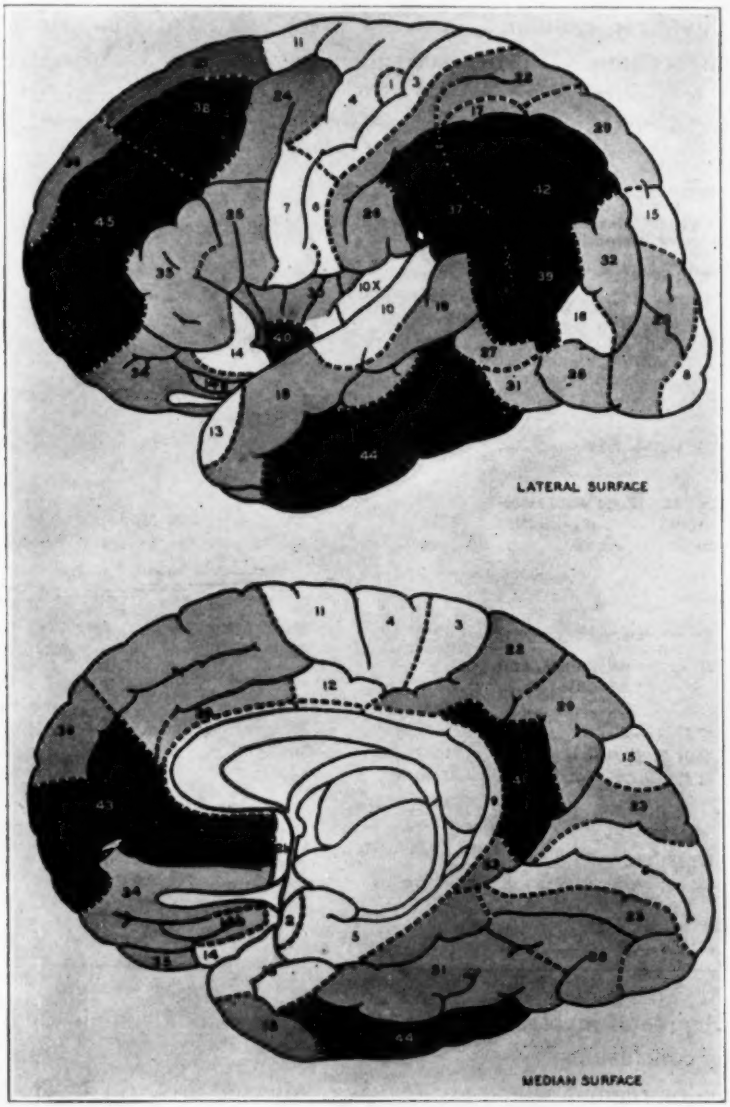


Fig. 10.—Myelogenic fields of Flechsig. Numerals indicate the order in which myelination develops. White areas denote the primordial group (fields *1* to *16*, which myelinate before birth); gray areas, the intermediate group (fields *17* to *36*, which myelinate during the first month of life), and black areas, the terminal group (fields *37* to *45*, which myelinate after the fifth week of life).

atrophy of the cingulate region may be associated with involvement of the temporal and parietal regions.

2. The major regions which regularly show only mild changes, and may be considered as "resistant," are: the supratemporal area; the presubiculum and the

cornu ammonis, and the postcentral, the occipital and the retrosplenial area. These regions correspond to the koniocortex of von Economo with its immediate surroundings, and physiologically they represent the sensory centers. It is noteworthy that the koniocortex proper, for example, the calcarine area, showed the least change, if any. In addition, area 4, or the motor cortex, usually remains uninvolved, but in our case 1 a part of the Betz cell area on the left side was encroached on.

3. The regions between the areas mentioned in 1 and those in 2 are inconstantly affected, an observation suggesting a more or less limited extension of the disease from the adjacent "susceptible" regions, such as premotor area 6 and the uncus formations.

We have also tested the genetic explanation advanced in the literature by comparing the charts in figures 8 and 9 with the myelogenic charts of Flechsig [15] (fig. 10). It may be seen that the resistant regions in our cases of Pick's disease correspond to the "primordial" fields, particularly to the "primary sensory spheres" (fields 1 to 10), of Flechsig. That this is only approximate may be explained by the fact that the latter fields occupy somewhat larger areas than the corresponding koniocortex of von Economo and area 4, with which the "resistant" regions can be better correlated. On the other hand, the "terminal" fields of Flechsig are regularly and maximally involved in cases of Pick's disease, so much so that it seems to correspond to the "primary foci of atrophy" aforementioned. The disease, however, usually occupies larger areas, extending beyond the "terminal" fields into some of Flechsig's "intermediate" fields. Also, there are such discrepancies as the severe involvement of the temporopolar and orbital parts of the inferior frontal region, which myelinate early, and, on the other hand, the minimal involvement of some of the later myelinating fields in the superior temporal and occipital gyri. Probably such discrepancies may be expected, since cytoarchitectonic and myelogenic studies fail to agree on some points and Flechsig himself stated that the myelogenic approach can demonstrate only general principles and may fail in details. Phylogenetically there is also considerable evidence that the affected regions are the predominantly "human" ones, or the last fields to develop in the course of evolution, while most of the resistant regions represent "homologous" fields, which are present in all species of mammals. Here, too, discrepancies exist, which may depend on the incompleteness of present knowledge or on secondary factors in the disease process.

In this discussion, the chief emphasis has been placed on the changes in the cortex. The much less common primary involvement of parts of the subcortex does not contradict the genetic interpretation and, in fact, may support it, as Löwenberg and his associates [7] have pointed out.

CONCLUSIONS

This study lends support to the view expressed by some previous investigators that Pick's disease is a heredodegenerative disorder. Such a conclusion is based on the definite pattern of dominant inheritance in the two families we report and on the evidence that the condition develops as a system disease in the genetically youngest cytoarchitectonic regions, with corresponding disturbances in the highest cortical functions. The relatively minor discrepancies in the anatomic picture can in no way invalidate the significance of the principal observations.

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15. Flechsig, P.: Anatomie des menschlichen Gehirns und Rückenmarks aus myelogenetischer Grundlage, Leipzig, Georg Thieme, 1920, vol. 1.

CONVULSANT SHOCK TREATMENT OF PATIENTS WITH MENTAL DISEASE BY INTRAVENOUS INJECTION OF ACETYLCHOLINE

ELECTROENCEPHALOGRAPHIC AND ELECTROCARDIOGRAPHIC OBSERVATIONS

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In 1939 Fiamberti [1] reported on the use of intravenous injections of acetylcholine chloride for the production of convulsions in treatment of the psychoses. It was stated that these convulsions were not as severe as those produced by the injection of metrazol and were, therefore, less apt to produce fractures, a complication which has been reported to occur frequently with the latter form of therapy.[2] In view of these considerations and because acetylcholine is known to play an important role in normal neurohumeral mechanisms,[3] it was thought desirable to extend the studies of Fiamberti.

An extensive literature is available on the effects of acetylcholine and its derivatives, both in animals and in man.

Carmichael and Fraser [4] stated that the rapid intravenous injection of 0.2 to 0.5 cc. of a 5 per cent solution of acetylcholine hydrochloride into normal human subjects produced a sense of obstructed breathing and cough, followed shortly by increased breathing, slowing of the heart and flushing of the skin. The minimal dose required to obtain these effects was 15 to 30 mg., and with somewhat larger doses the heart might be stopped for a few seconds. Administration of the same minimal dose of acetylcholine hydrochloride one-half hour after the injection of 0.85 mg. of physostigmine salicylate (the purpose of the latter being to prevent the rapid inactivation or destruction of the acetylcholine) produced cardiac arrest for eleven and eight-tenths seconds in 1 case and for eight and six-tenths seconds in another. This was followed, in the former case, by a convulsion and by auricular fibrillation, which lasted two hours. It is probable that the convulsions produced by Fiamberti [1] by the rapid intravenous injection of larger doses of

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1. Fiamberti, A. M.: Sull meccanismo d'azione terapeutica della "burrasca vascolare" provocata con derivati della colina, Gior. di psichiat. e di neuropat. **67**:270, 1939; Riv. oto-neuro-oftal. **17**:265, 1940.

2. Polatin, P.; Friedman, M. M.; Harris, M. M., and Horwitz, W. A.: Vertebral Fractures Produced by Metrazol-Induced Convulsions in the Treatment of Psychiatric Disorders, J. A. M. A. **112**:1684 (April 29) 1939; Vertebral Fractures as a Complication of Convulsions in Hypoglycemic Shock and Metrazol Therapy in Psychiatric Disorders, ibid. **115**:433 (Aug. 10) 1940. Wespi, H.: Ein Fall von spontaner Wirbelfraktur im Cardiazolanfall, Schweiz. Arch. f. Neurol. u. Psychiat. **42**:404, 1938.

3. Brown, G. L.: Transmission at Nerve Endings by Acetylcholine, Physiol. Rev. **17**:485, 1937. Eccles, J. C.: Synaptic and Neuro-Muscular Transmission, ibid. **17**:538, 1937.

4. Carmichael, E. A., and Fraser, F. R.: Effects of Acetyl Choline in Man, Heart **16**:263, 1933.

acetylcholine chloride (100 to 600 mg.) were due to similar pronounced temporary disturbances in circulation.

In epileptic patients, Williams [5] found that the intravenous injection of 30 to 60 mg. of acetylcholine hydrochloride in a volume of 1 cc. produced an increase in the number of "epileptic discharges" in the electroencephalogram, and in 1 patient 30 mg. also induced a clinical attack, without any appreciable bradycardia. The larger dose of acetylcholine produced only a short period of cardiac arrest of two seconds. Six injections of acetylcholine hydrochloride in normal persons produced no changes of an epileptic character in the electroencephalogram.

Since the onset of the "epileptic discharges" in the electroencephalogram occurred within seven seconds after the intravenous injection, it appeared that the period might be too short for the drug to reach the central nervous system and that the results obtained might be secondary to effects produced elsewhere in the body, such as disturbances in respiration. However, various experiments which were carried out did not establish the validity of this assumption.

In the present studies, acetylcholine chloride was administered to a group of patients with mental disorders in order to induce convulsions as a therapeutic measure. The dose of acetylcholine was increased until loss of consciousness was obtained. Fiamberti found that 100 to 600 mg. was required for this effect. In our patients the required dose also varied approximately between these limits.

PROCEDURE

All the patients received the regular medical examination, which included electrocardiographic studies. The effect of pressure on the carotid sinus was also determined prior to treatment, in conjunction with the simultaneous taking of electrocardiographic records. This was done in order to exclude patients with a hypersensitive carotid sinus. The initial dose of acetylcholine chloride, irrespective of the weight of the patient, was 70 mg. This amount was increased by 20 mg. or more with each injection until a dose adequate to produce loss of consciousness for about forty-five seconds was reached. This amount was then used in subsequent injections with that patient. Treatments were administered daily, five times a week except over the week end.

The solution of acetylcholine chloride was freshly prepared immediately before injection by dissolving the crystals, which were supplied in sealed glass ampules,[6] in sterile distilled water so as to make a 10 per cent concentration. The injections were made into the anterior cubital vein as rapidly as possible, which was about two to three seconds by the stopwatch.

Electrocardiographic and electroencephalographic records were taken immediately before, during and after the injection of acetylcholine, both at the beginning and at the end of a course of treatments.

The electrocardiograph used was a string galvanometer of the Cambridge research type. On some of the patients simultaneous electroencephalograms and electrocardiograms were also taken by means of the amplifying and recording units of the electroencephalograph.

Electroencephalograms were made by means of a two channel ink-writing, push-pull amplifying system with an attached recorder. The bipolar method of recording variations in potential was utilized. Preliminary records prior to treatment were taken with fronto-occipital (right and left), motor-occipital (right and left) and frontomotor (right and left) leads. In addition, tracings were taken with transfrontal, transmotor and transoccipital leads.

In order to study the immediate effects of injection of acetylcholine, one channel was used to record the brain potentials with the left motor-occipital lead, while the second channel was used to obtain a simultaneous electrocardiogram. For the latter purpose, two electrodes were attached over the sternum at the levels of the second and the third intercostal space respectively. Maximum amplification was used for recording brain potentials, while for obtaining the electrocardiogram amplification was materially reduced in order to adjust it to the higher electrical potentials produced by the heart.

5. Williams, D.: Effect of Cholin-Like Substances on Cerebral Electrical Discharges in Epilepsy, J. Neurol. & Psychiat. **4**:32, 1941.

6. Dr. R. J. Floody, of Hoffmann-LaRoche, Inc., supplied the acetylcholine chloride used in these studies.

OBSERVATIONS

Immediately after the injection of an adequate dose of acetylcholine there were a sense of malaise and desire to cough. The face and lips usually turned pale. The patient frequently sat up for a few seconds because of the disagreeable sensation of choking or oppression in the chest and then fell back unconscious. Usually there was a tonic, extensor spasm of the body at this time, associated with or followed by mild twitching of the face and upper extremities. Strong clonic contractions, such as are obtained with metrazol or electric shock, did not occur. Usually, also, there were increased salivation and lacrimation, and at times incontinence of the bladder and of the bowels.

The loss of consciousness was always associated with cardiac arrest. This usually lasted from thirty to fifty seconds. Consciousness returned within a few seconds after the heart beat reappeared. No amnesia or abnormal plantar reflexes were noted, such as are usually obtained with the other forms of convulsant therapy. The electrocardiographic observations will be reported in detail in a separate communication.

Variability in Convulsant Doses of Acetylcholine and Number of Treatments Administered to Eight Patients with Mental Disorders

Patient	Case Number	Age, Yr.	Sex	Weight, Kg.	Diagnosis *	Convulsant Dose of Acetylcholine Chloride, Mg.	Number of Treatments
M. A.	1	28	F	73	D. P. H.	480	34
L. D.	2	18	F	62	D. P. C.	300	61
R. C.	3	56	M	74	I. M.	220	3
B. S.	4	20	F	56	D. P. H.	380	57
H. R.	5	29	M	62	D. P. P.	500	23
R. B.	6	19	F	50	M. D. D.	380	31
S. M.	7	25	F	55	D. P. C.	390	19
O. B.	8	16	F	50	D. P. C.	280	4

* D. P. H. indicates dementia praecox, hebephrenic type; D. P. C., dementia praecox, catatonic type; D. P. P., dementia praecox, paranoid type; M. D. D., manic-depressive psychosis, depressed type, and I. M., involutional melancholia.

A total of 232 injections were given to 8 patients who were mentally ill. With patient 8 treatment had to be discontinued early because of the difficulty in finding satisfactory veins for injection. In another patient, R. C., aged 56, the injection of acetylcholine in a dose sufficient to induce cardiac arrest and loss of consciousness produced precordial pain, lasting several minutes. Although this patient's electrocardiogram was normal and he gave no history suggestive of coronary disease, in view of his age, it was considered unsafe to continue with the treatment. The patient subsequently had a spontaneous recovery.

The other patients received from 19 to 61 treatments (table). R. B. was suffering from an agitated depression. She received 31 treatments, without improvement. She was then given a short course of electric shock therapy, which resulted in prompt and sustained improvement.

None of the patients showed any improvement with acetylcholine convulsant therapy. Practically all the patients displayed fear of the treatment, since there was no amnesia for the disagreeable sensations which occurred prior to the loss of consciousness. Control, pretreatment electroencephalograms were taken on all patients, and only 1 of these (the record of R. C.) exhibited a mild abnormality in the pattern, as evidenced by some irregular wave forms and frequencies, and occasionally 7 to 8 per second potentials (bilateral); all other control records were

within normal limits. None of the records taken after termination of the entire course of treatments showed any appreciable alteration in the electroencephalographic pattern other than that observed prior to administration of acetylcholine.

It was noted that when the dose of acetylcholine was not sufficient to produce unconsciousness, cardiac arrest did not exceed approximately seven seconds. In such instances there were no appreciable changes in the electroencephalogram. This is illustrated in the case of R. C. (fig. 2, graph 3 *A*), in which, after the

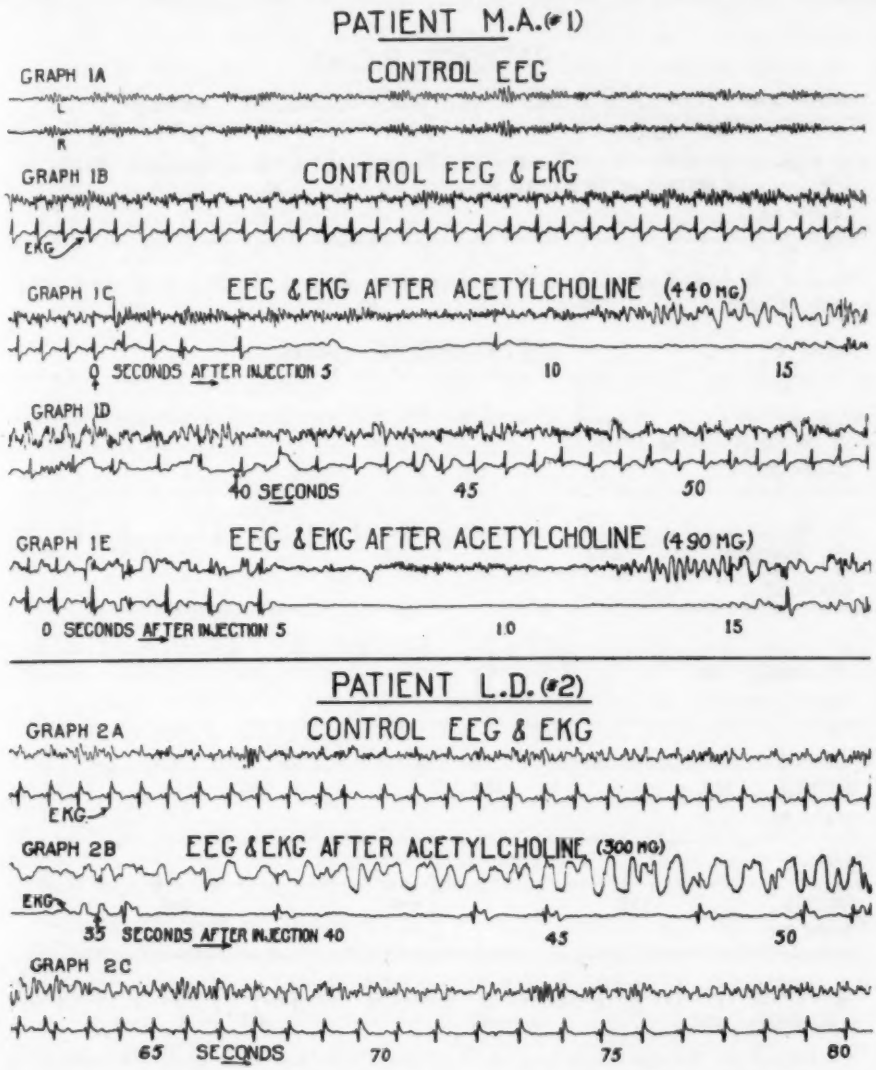

Fig. 1.—Effect of injection of convulsant doses of acetylcholine chloride on the electroencephalograms and electrocardiograms of patients M. A. and L. D. Note the electrocardiograms in graphs 1 *C* and 1 *E*, showing the cardiac arrest, and the electrocardiogram in graph 2 *B*, showing the bradycardia. The abnormal, slow, high potential brain waves are seen in the electroencephalograms of graphs 1 *C* and 1 *E* after about seven to eight seconds of cardiac arrest, and in graph 2 *B* these changes are pronounced and persist during the period of bradycardia following one of cardiac arrest.

injection of 80 mg. of acetylcholine chloride, there was cardiac arrest for about five seconds, with apparently no resulting disturbance in the electroencephalographic

pattern. The variation in potentials noted in the electroencephalographic record between one to seven seconds after injection (graph 3 *A*) are largely artefacts due to movements.

In the case of M. A. (fig. 1, graphs 1 *C* and 1 *E*) it will be noted that after a period of cardiac arrest of approximately seven to eight seconds abnormal potentials appeared. At about this point unconsciousness usually occurred and lasted for the entire period of cardiac arrest. The abnormal potentials usually persisted for five to thirty seconds after regular cardiac rhythm was established,

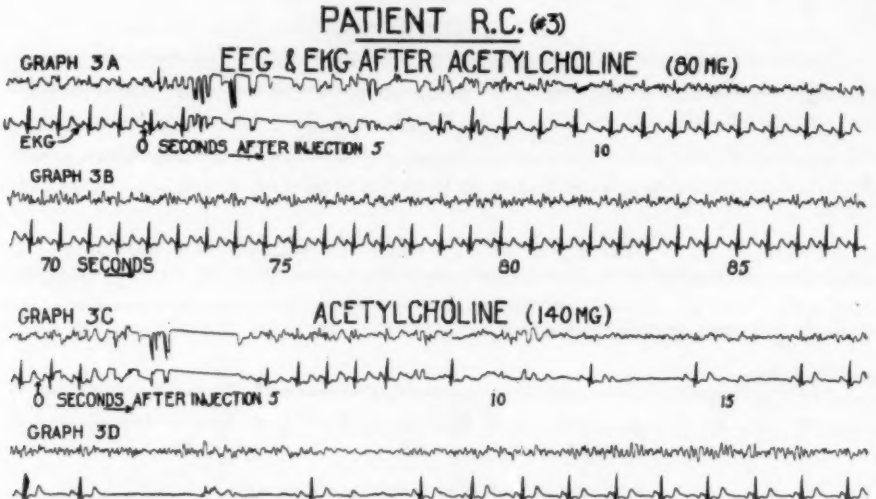

Fig. 2.—Effect on the electrocardiogram and the electroencephalogram of patient R. C. of doses of acetylcholine chloride which did not produce cardiac arrest, but did cause bradycardia and a decided fall in blood pressure. Compare with figure 1.

during which time the pattern gradually returned to its preshock form. It will be noted in the record for L. D. (fig. 1, graph 2 *B*) that the abnormal waves persisted during the period of bradycardia following an interval of cardiac arrest of about thirty seconds, not shown in the graph, during which interval consciousness was lost. However, with the appearance of regular cardiac rhythm (graph 2 *C*), alpha waves soon reappeared, and the slow waves of high amplitude no longer occurred.

It may be noted that consciousness had returned during the period of bradycardia seen in graph *2 B*.

The records for R. C. (fig. 2) illustrate the effect of the production of prolonged bradycardia, without cardiac arrest, after the injection of 140 mg. of acetylcholine chloride. During the first thirty seconds after the injection, bradycardia with irregular rhythm occurred, the rate varying from 15 to 60 beats per minute (graphs *3 C* and *3 D*). This period was followed by bradycardia with an essentially regular rhythm, of 50 to 60 beats per minute, lasting about twenty minutes (graphs *3 E*, *3 F* and *3 G*). After this the heart rate rose gradually to 72 per minute (graph *3 H*). During the period of bradycardia moderate changes appeared in the electroencephalogram, consisting chiefly of occasional, random waves of a 6 to 8 per second frequency, with preservation, however, of regular alpha activity. These slow waves disappeared during the period shown in graph *3 H*, as the heart rate increased. It should be noted, also, that during the period of bradycardia the blood pressure fell to 80 systolic and 0 diastolic. However, the condition of the patient appeared satisfactory, and the blood pressure rose to 94 systolic and 64 diastolic during the period shown in graph *3 H*.

COMMENT

As was previously pointed out, doses of acetylcholine chloride which did not produce appreciable effects on the circulation were also without effect on the electroencephalogram in the cases studied. This observation is similar to that of Williams,[5] namely, that acetylcholine produced no effect on the electroencephalogram in clinically normal subjects, although the doses of 30 to 60 mg. of acetylcholine hydrochloride which he used were substantially less than ours. Even when the dose was sufficiently large to produce appreciable bradycardia with a drop in blood pressure, as described in the case of R. C., only moderate changes occurred in the electroencephalogram. One cannot decide whether these changes were due to acetylcholine itself or to the disturbance in circulation or to both. We are inclined to believe that the circulatory disturbance might be sufficient to produce such changes. The pronounced changes in the electroencephalogram occurred only with prolonged cardiac arrest. Since the cardiac arrest occurred within four seconds or less after the injection of acetylcholine, it is unlikely that any appreciable amount of the drug was able to reach the central nervous system; therefore the pronounced electroencephalographic changes which make their appearance within ten seconds after cardiac arrest are most likely due to interference with circulation in the brain. The persistence of a notable abnormality in the electroencephalogram after the heart beat was resumed may also be due to the effects produced by the immediately preceding arrest in circulation. Whether any acetylcholine was still present in the blood stream at this time, and was a contributing factor to the production of the persisting abnormalities in the electroencephalogram, is not yet determined. However, the interruption of the circulation of the brain for relatively short periods is known to produce similar severe disturbances in the electroencephalographic pattern.

The absence of amnesia, of signs of disturbance of the pyramidal tracts, and of any prolonged changes in the electroencephalogram following convulsions produced by acetylcholine is in contrast to the presence of such changes following convulsions produced by metrazol or electric shock.

The failure of R. B. to respond to 31 injections of acetylcholine chloride and her prompt recovery after only a few electric shock convulsions also point to the notable differences in the changes produced in the body by the two forms of

convulsant therapy. The disagreeable sensations produced by the injections of acetylcholine and the fear of treatment are other points of difference. While psychologic factors probably play a role in the shock therapies, they do not appear to constitute the most important factor in some cases. In the case of R. B. the psychologic effects of the injections of acetylcholine must have been more decided than those of electric shock; still, only the latter treatment was effective. Cases such as these indicate that the physicochemical changes produced by the various types of shock therapy differ and that these differences are probably significant.

Some investigators[7] have expressed the opinion that the essential common factor in the various forms of shock therapy is anoxia. The period of complete cardiac arrest following convulsive doses of acetylcholine is thirty to fifty seconds, which is equal to the average duration of a convulsive seizure produced by electric shock or metrazol. Since the heart continues to beat during the latter forms of treatment, it is likely that the anoxia is more complete during the acetylcholine treatment, in which the circulation is completely arrested. (The complete arrest of the circulation was confirmed by retinoscopy.) This observation indicates that the anoxia alone is not the deciding factor in treatment and is in keeping with the suggestion previously made that the organic or physicochemical changes produced also probably differ significantly in the different forms of shock therapy.

Although no ill effects were observed with the large doses of acetylcholine, the production of cardiac arrest by intravenous injection is a drastic procedure. Its use as a form of therapy would be justified only if it were effective where the other forms of shock therapy had failed. However, our studies fail to disclose any favorable effect for which it could be recommended. The investigation seems to be of value, however, for the additional information it yields regarding some of the mechanisms involved in shock therapy.

SUMMARY AND CONCLUSIONS

1. The effect on patients with mental disorders of the intravenous injection of large doses of acetylcholine chloride has been investigated.

2. These doses of acetylcholine produced mild convulsions associated with cardiac arrest and loss of consciousness, lasting thirty to fifty seconds.

3. A series of convulsions produced by acetylcholine had no ameliorating effect on the mental condition of the patients studied.

4. The significance of the studies with regard to the mechanisms of shock therapy in general is discussed.

5. Acetylcholine convulsant therapy does not appear to be a desirable procedure.

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7. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Brain Metabolism During the Hypoglycemic Treatment of Schizophrenia, Science **86**:271, 1937. Harris, M. M.; Blalock, J. R., and Horwitz, W. A.: Metabolic Studies During Insulin Hypoglycemic Therapy of the Psychoses, Arch. Neurol. & Psychiat. **40**:116 (July) 1938.

AUTONOMIC BALANCE IN PATIENTS TREATED WITH INSULIN SHOCK AS MEASURED BY MECHOLYL CHLORIDE

A PRELIMINARY REPORT

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RATIONALE

Pavlov [1] and Cannon [2] made important contributions to knowledge of the autonomic nervous system, in which they pointed out the significance of this system in the maintenance of a constant equilibrium (homeostasis) in the body. Since then much work has been done to determine the activity of the autonomic nervous system in schizophrenia, with the thought that such a study may throw light on this serious personal and social problem.

One has only to mention La Mar [3] and Henry,[4] among the many who have worked on this problem. The results of these investigators pointed to certain types of deviations, or at least tendencies to deviations, in the autonomic nervous system of schizophrenic patients which differentiate their mental reactions or behavior patterns from those of other persons. Such workers, however, made their observations on a relatively static condition, while the equilibrium of the autonomic system, as conceived by Pavlov and Cannon, is dynamic. They measured the blood pressure level,[5] changes in the gastrointestinal tract [4] and alterations in the pulse rate [3] at a given moment, or they noted a single reaction to a stimulating drug. On the other hand, a review of Dunbar's [6] extensive compilation of the literature, reveals that the physiologic processes connected with psychic changes could be more accurately investigated if a given physiologic activity was studied as part of a dynamic equilibrium. Similar approaches to organic pathologic changes, e. g., the dextrose tolerance test, have brought significant results.

In the present project it was decided to study the autonomic nervous system from the point of view of the equilibrium which is maintained by the constant interplay of its two component parts, the sympathetic and the parasympathetic. It was felt that the stability of this equilibrium is its most significant characteristic and that, therefore, a study of the mode by which the autonomic nervous system maintains its own equilibrium would be significant. If the system were thrown

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The mecholyl chloride used in this research was supplied by Merck & Co., Inc., Rahway, N. J.

Read at the Eighty-Sixth Meeting of the New York Society for Clinical Psychiatry, March 11, 1943.

1. Pavlov, I. P.: Conditioned Reflexes, New York, Oxford University Press, 1927.

2. Cannon, W. B.: The Wisdom of the Human Body, New York, W. W. Norton & Company, Inc., 1932; Autonomic Neuro-Effector Systems, New York, The Macmillan Company, 1937.

3. LaMar, N.: Histamine Reactions in Psychoses, A. Research Nerv. & Ment. Dis. Proc. (1929) **11**:236, 1931.

4. Henry, G. W.: Roentgenologic Observations of Gastrointestinal Conditions Associated with Mental Disorders, Am. J. Psychiat. **7**:135, 1928.

5. Palmer, H. D., and Appel, K. E.: Ephedrine Circulatory and Glycemic Reactions in Psychoses, A. Research Nerv. & Ment. Dis., Proc. (1929) **11**:226, 1931.

6. Dunbar, F.: Emotions and Bodily Changes, New York, Columbia University Press, 1938.

out of balance temporarily, the ease with which this is effected, and the mode and rate of recovery to its original balanced state, that is, the method of its own readjustment, could be studied. A description of these features would then be a description of the activity of the autonomic nervous system as it maintains homeostasis in the given person.

The drug mecholyl chloride, a choline derivative, was chosen to stimulate the parasympathetic portion of the autonomic nervous system, and thus unbalance the whole system. It has been reported that mecholyl chloride acts rather specifically on the parasympathetic portion and that the results of its injection are fairly constant.[7] These results consist of a temporary lowering of the systolic and diastolic pressures, an increase in pulse rate, flushing, increased salivation, lacrimation and perspiration. After some experimentation, it was decided to study the effect of mecholyl on autonomic balance through the medium of the systolic blood pressure. As is well known, the systolic blood pressure is maintained by an interplay between the two parts of the autonomic nervous system.[8] Thus, a curve illustrating the changes in systolic blood pressure at regular, frequent intervals would describe changes occurring in the equilibrium of the autonomic nervous system.

It was then decided to relate this study to schizophrenic patients by studying the autonomic balance of such persons before and after insulin shock therapy. Since the advent of this treatment much work has been done in an attempt to understand the mechanism of improvement which it brings about. Many investigators have noted changes in the sympathetic system at the conclusion of treatment.[9] In the present study an attempt is made: (1) to observe such autonomic changes by means of the "mecholyl curve"; (2) to note whether any significant alterations can be correlated with changes in the clinical picture after treatment, and (3) to note whether improvement in the patient is concomitant with improvement in autonomic balance.

METHOD

The patients studied were selected from the group in the insulin service of the Brooklyn State Hospital. Both male and female patients were observed and were taken in the order in which they were received in the service for treatment. The formal diagnosis in all cases was schizophrenia, catatonic type. The only contraindications to selection were a history of bronchial asthma or a pathologic condition of the heart. They were usually tested late in the afternoon or evening, not immediately after mealtime. The blood pressure and pulse rates were read every two minutes until the level was stabilized so that three successive readings did not vary from one another more than 6 mm. of mercury. Next, mecholyl chloride was injected subcutaneously in a dose equivalent to between 0.11 and 0.12 mg. per pound (0.5 Kg.) of body weight. Then the blood pressure, both systolic and diastolic, and the pulse rate were recorded every two minutes. Likewise, note was made of the other clinical reactions, such as flushing, increased salivation, perspiration and lacrimation. The test was concluded when the pulse rate returned to the original level and the blood pressure no longer showed fluctuations of more than 6 mm. of mercury, or usually thirty minutes after injection of the

7. Myerson, A.; Loman, J., and Dameshek, W.: Physiologic Effects of Acetyl-Beta-Methylcholine (Mecholyl), Am. J. M. Sc. **193**:198, 1937. Myerson, A.; Loman, J., and Rinbel, M.: Human Autonomic Pharmacology, ibid. **194**:75, 1937. Myerson, A., and others: Human Autonomic Pharmacology, Am. Heart J. **16**:329, 1938. Page, I. H.: Acetyl-Beta-Methylcholin (Mecholin): Observations Concerning Its Action on Blood Pressure, Skin Temperature and Heart, as Exhibited by Electrocardiogram of Hypertensive Patients, Am. J. M. Sc. **189**:55, 1935.

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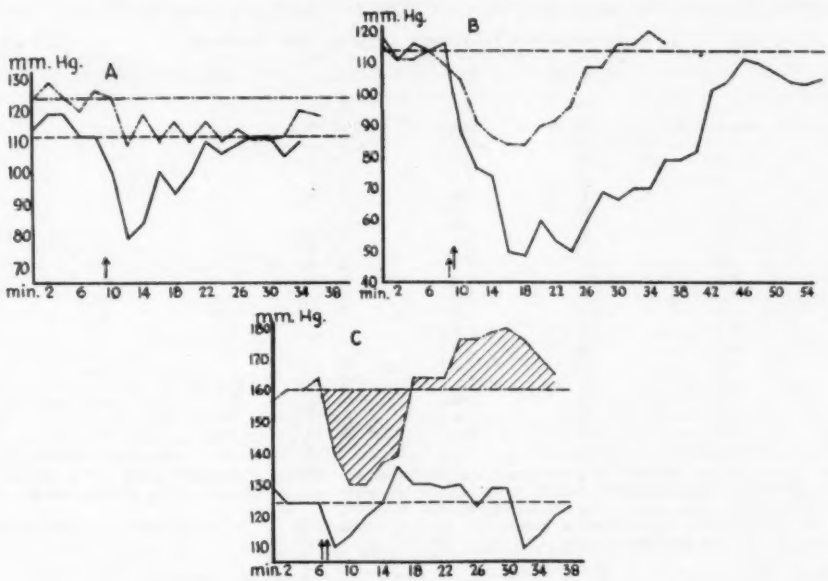
9. Gellhorn, E.: Action of Hypoglycemia on Central Nervous System and Problem of Schizophrenia from Physiologic Viewpoint, J. A. M. A. **110**:1433 (April 30) 1938. Farrell, M. J., and Vassaf, E.: Effect of Insulin Shock on Heart and Blood Pressure in Treatment of Schizophrenia, Arch. Neurol. & Psychiat. **43**:784 (April) 1940. Hoffman, H. A.: Pharmacologic Aspects of Shock Therapy, J. Nerv. & Ment. Dis. **95**:18, 1942.

drug. Atropine sulfate, in a dose of 0.8 mg. was always on hand to counteract any untoward reactions. The readings of the systolic blood pressure were then plotted in the form of a graph against the time, expressed in minutes (figure). One test was conducted one day before the institution of treatment, and the final test was made after the conclusion of treatment. At least forty-eight hours was allowed to elapse after the injection of the last dose of insulin in order to permit the excretion of the drug, the presence of which in the body might distort the reaction to mecholyl chloride.

To exclude as many extraneous stimulating factors as possible, the tests were conducted in fairly quiet surroundings, and the patient was not spoken to except to explain some of the reactions which occurred, such as flushing, perspiration and palpitation. In some cases, those in which the blood pressure fluctuated freely during the period of stabilization, a sudden noise was introduced to determine its effect on the blood pressure. During the acute illness the patients seemed so preoccupied with their own thoughts that there was no notable reaction to sudden stimuli.

RESULTS

At the time of writing this investigation is still under way, so that the present report can be considered only as preliminary. For the moment, the mecholyl curves



Sample curves, showing variations in systolic blood pressure after injection of mecholyl. The solid line indicates the curve of fluctuations in systolic tension before institution of insulin shock; the line of dots and dashes, the curve after completion of treatment.

The area of the curve is the shaded portion; the blood pressure, in millimeters of mercury, is plotted on the ordinate; the time, in minutes, on the abscissa. The curves in *A* are for patient 30; the curves in *B*, for patient 7, and the curves in *C*, for patient 16. The post-treatment curve in *B* shows the notable improvement in the clinical condition of patient 7, and the curve in *C*, the moderate improvement in the clinical condition of patient 16.

of 33 patients as determined before and after insulin shock therapy are reported. Before the results before and after treatment are compared, the curves in general (figure *A*) may be briefly described. As seen in the graph, immediately after the injection of the mecholyl chloride (the arrow points to the time of injection) there was a decrease in systolic tension. The amount and rate of this decrease varied for each curve. After reaching a low point, the curve usually began to rise immediately. There were, however, some curves which remained at the low level for several minutes (figure *B*). Then, from the low point, there was a gradual rise in blood pressure, at varying rates, until the original level of tension was

reached, or in some cases the pressure rose above this level at first and then returned to the original level (figure *C*).

The following items may be considered in describing the curve: (1) the amount of the drop in systolic tension; (2) the time required for the drop; (3) the time elapsing before the curve begins to recover; (4) the rate of recovery; (5) the total time elapsing between the injection and the end of the test, and (6) the course of the curve.

In the present study, the most significant aspects of the curves are the rate of recovery from the low point and the total area which the curve involves, the latter taking into consideration the path of the curve. The rate of recovery is considered as the increase in blood pressure per minute shown by the recovery portion of the curve, i. e., from its lowest point to the level of the basal blood pressure. The area which the curve includes is bounded by the curve itself and

TABLE 1.—*Improvement in Curves After Insulin Treatment* *

Patient No.	Curve Before Treatment		Curve After Treatment		Change in Curve	Patient's Condition After Treatment †
	Area	Rate	Area	Rate		
1	52	1.9	53	2.5	+	I ?
3	116	1.05	58	1.3	++	M. I.
5	67	2.1	37	1.5	+	I.
7	160	1.7	39	2.5	++	M. I.
8	16	2.2	16	4.3	+	M. I.
9	42	1.7	+1	1.0	+	N. C.
10	18	1.4	0	2.7	++	I ?
12	82	1.8	29	1.0	+	N. C.
16	2	2.3	2	3.7	+	M. I.
20	30	0.66	17	1.8	++	M. I.
23	72	2.1	59	2.0	+	M. I.
24	70	1.2	39	2.6	+	N. C.
26	+5	1.2	19	1.8	+	M. I.
31	18	1.8	7	3.0	++	N. C.
34	14	1.6	?	2.3	+	I.
35	73	2.6	37	1.5	+	I.
37	57	1.2	21	1.3	+	N. C.
41	16	0.6	22	2.3	+	M. I.
43	33	2.1	45	3.0	+	M. I.
45	34	2.6	74	4.0	+	M. I.

* In this table and in table 2, improvement is indicated by either a smaller area or a higher rate of recovery; + denotes improvement either in area or in rate of recovery; ++, improvement in both; — no improvement in one, and — — no improvement in either.

† M. I. indicates much improvement clinically; I., improvement; I ?, questionable improvement, and N. C., no change in the clinical picture.

a line drawn through the level of the basal blood pressure (the horizontal broken line). For this report, the area was measured by counting the number of squares within the aforementioned boundaries. That part of the curve which was above the basal line was considered as representing plus values and that which was below the line as representing minus values, so that the area is an algebraic sum of the squares involved within the curve. This description of the curve was devised by Pratt,[10] who also worked with mecholyl (figure *C*).

When the curves taken before and after insulin shock treatment are compared, it is noted that 20 subjects (66 per cent) showed what was considered improvement in the curve. Four others, or 12 per cent, showed a greater reactability to mecholyl chloride; i. e., they responded better to stimulation after shock treatment. In an attempt to correlate improvement in the curve with improvement in the clinical picture, it is noted that of the 20 patients with curves, denoting improved reactability, 13 (62 per cent) showed definite clinical improvement and 2 others had improved sufficiently to leave the hospital. Only 5 patients (25 per cent) showed no clinical improvement (table 1).

10. Pratt, D.: Personal communication to the author.

On the other hand, of the total number of patients who improved clinically, 17, only 4 had curves which did not change or showed a poorer response after treatment. Twelve of the 17 patients showed improvement in the curve, and the curve for 1 patient indicated better reactability of the autonomic nervous system, and hence a more flexible and better functioning one (table 2).

Of a little more significance is the evidence obtained from the extreme curves, i. e., the curves which denote sluggishness in return of the blood pressure to the original stable level, for example, the curves for patients 3, 5 and 7 and the curve in *B*. These are the curves which show a slow rate of recovery and which bound the largest areas. In the present report, there were 10 patients with such curves. For 6 of these patients the curves after insulin shock treatment showed improvement. The rate of recovery was more rapid; the total time elapsing before the arterial tension returned to the original level was shortened, and the area bounded by the curve was reduced. For 4 of the 10 patients the curves showed slight or no change. The correlation between improvement in the clinical picture and a change in the curve was positive for 8 of the 10 patients. When the curve showed

TABLE 2.—*Change in Curves of Patients Who Improved After Insulin Shock Therapy*

Patient	Curve Before Treatment		Curve After Treatment		Change in Curve
	Area	Rate	Area	Rate	
3	116	1.05	58	1.3	++
4	40	6.0	85	2.2	−−
5	67	2.1	37	1.5	+
7	160	1.7	39	2.5	++
8	16	2.2	16	4.3	+
16	2	2.3	2	3.7	+
20	30	0.66	17	1.8	++
22	12	3.3	23	1.4	−−
23	72	2.1	59	2.0	+
25	1	3.0	0	1.0	−
26	+5	1.2	19	1.8	+
27	+4	3.0	12	3.4	−
34	14	1.6	?	2.3	+
35	73	2.6	37	1.5	+
41	16	0.6	22	2.3	+
43	33	2.1	45	3.0	+
45	34	2.6	74	4.0	+

improved reactability, the patient exhibited clinical improvement. On the other hand, when the curves showed no, or only slightly, faster return to balance, the patient showed no, or only slight, improvement in the clinical picture.

COMMENT

The results thus far show certain changes in the maintenance of homeostasis by the autonomic system after insulin shock therapy. There was a tendency to improvement in maintaining the autonomic stability after completion of such treatment. This was especially noted in patients who showed clinical improvement. The change for the better was noted in improved sympathetic activity.

The part of the curve continuing from the low point until the end can be considered to represent preponderance of sympathetic activity. Therefore, when changes in sympathetic activity after insulin shock therapy are described, this part of the curve is referred to. The increased rate of recovery, the reduction in the time required to return to the original level of arterial tension and the continuation of the curve above the original level, all tend to show an increase in activity of the sympathetic portion. This part of the autonomic nervous system, after treatment, becomes more capable of restoring the whole system to its original stable level, once it has been unbalanced by a drug activating the parasympathetic portion.

Evidence of such improvement in autonomic activity, especially of the sympathetic portion, has been noted by other workers in studying a similar problem.[9] It is suggested, therefore, that the study of the autonomic balance by means of mecholyl is an addition to the methods by which functioning of the autonomic system can be investigated. This method is relatively simple and can be carried out by members of the personnel after only a little training. In the present study no untoward reactions have resulted from the use of mecholyl chloride. Future projects, combining studies of the adrenergic and the cholinergic substances liberated and the concomitant mecholyl curves, should further point out the significance of the type of curve described here. Furthermore, this method of study of the autonomic system is concerned with an important aspect of this system, its ability to maintain a dynamic equilibrium in human behavior.

Another question raised in this study is one of fundamental importance in any psychosomatic approach to medical problems. Are these changes in autonomic balance, noted after insulin shock, the direct influence of the shock treatment on autonomic balance, which, in turn, brings about such neural and other bodily changes as to improve the clinical picture? Or is it that, whatever the mechanism that brings about improvement, the change in the subject's behavior and the improved emotional reactions influence the autonomic activity? These questions can be answered only by further studies to determine whether similar improvements in autonomic balance can occur after changes in emotional states without insulin shock therapy, for example, those produced by other shock therapies. This raises the possibility of one's learning more about the somatic fragments in total behavior, especially in psychiatric states, by means of the specific changes in autonomic balance induced in a given subject. Again, such a study enables one to note the type of a balance present with a given somatic complaint, e. g., urticaria, asthma or vomiting, which in itself is apparently associated with a psychic factor.

The results of the present project emphasize that an alteration in the balance and function of the autonomic system occurs with a change in the mental picture. Physiologically, there is a better reaction to stimuli with improvement in response to psychic stimuli. Previous to shock treatment the reactions were frequently slow, especially in patients with curves of the more extreme type previously cited, while after improvement from therapy the reactions were more rapid.

From a broader point of view, the physiologic and the psychic aspects of a reaction type show certain correlations, as has been noted by other investigators.[11] In patients treated with insulin shock, notable changes in behavior may be observed in a short time. This permits the practical possibility of studying concomitant autonomic and mental changes and of obtaining a clearer conception of autonomic function in mental illness. There occurs, also, the practical question of the prognostic value of such a test. Is it possible to foretell whether persons with certain types of curves will benefit more from insulin shock therapy than will others? Is it possible to predict the length of the course of insulin treatments? The questions cannot be answered at this time. However, the patients who have been tested by the mecholyl method thus far are under observation, and only more time and experience will give us the answers.

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SUMMARY

1. Another method of approach to the study of autonomic function in schizophrenic patients treated with insulin shock was undertaken. This method emphasizes the autonomic system as a functioning unit maintaining homeostasis (a dynamic equilibrium).

2. By means of injections of mecholyl chloride the changes in autonomic balance before and after insulin shock therapy were recorded.

3. In patients showing definite clinical improvement, there was noted improved ability on the part of the autonomic system to maintain its own balance, as well as a more rapid compensatory reaction to stimulation. The activity of the sympathetic system, especially, showed improvement.

4. It is suggested that this method is a relatively simple mode of studying autonomic activity.

5. Several suggestions in connection with a psychosomatic understanding of psychiatric problems were made, the possibility of the study of such problems being increased with the advent of insulin shock therapy.

Brooklyn State Hospital.

NATURE OF PAINFUL VASODILATATION IN CAUSALGIC STATES

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CHICAGO

During times of war certain syndromes, relegated to nonrecognition or oblivion in peacetime, require renewed emphasis. Among these is a peculiar vasomotor disturbance, for which a generally accepted name is lacking. It is my belief that Vulpian's [1] *état physiopathique,* Weir Mitchell's [2] causalgia, Sudeck's [3] atrophy, Leriche's [4] post-traumatic painful osteoporosis, the peripheral trophoneurosis [5] and the chronic traumatic edema [6] are only different manifestations of an essentially identical vasomotor disturbance. The diagnosis of this condition should be made early, and its differentiation from compensation neurosis, malingering and atrophy due to inactivity should be attempted, as the success of treatment is mainly dependent on the stage of the disease at which adequate treatment is undertaken.

Roughly, three stages of this syndrome are recognizable. In the first stage severe, persistent pain of a burning character with paroxysmal exacerbations due to jarring, air currents or emotional upsets is typical. If the injured limb is properly immobilized, uninfected and seemingly on the way toward normal repair, such complaints should make one suspicious of early reflex dystrophy. At this stage, the extremity is warm and dry; the subcutaneous and periarticular spaces are edematous, and the muscles are spastic in their effort to splint the wrist or ankle. Studies of the blood flow and oscillometric curves indicate increased circulation to the injured part. At this stage, the pain is closely limited to the site of the injury and its spreading character is not evident, nor is there any osteoporosis, which does not seem to appear unless continuous hyperemia has been present for four to six weeks.

The syndrome may cease to develop at this point, or its spread may be successfully aborted by adequate therapy; but it may progress to a second stage. Here, the periarticular edema has spread for some distance; the part is not as warm or flushed as it was earlier, and it may become hard, cyanotic and cold to the touch. The joints are stiff, and the muscles are becoming atrophic. Spotty atrophy of the bone is evident. The blood flow is not as active as in the first stage, but there is still a greater tendency to vasodilatation than in the uninjured limb. The pain

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6. Klassen, P.: Ueber das chronische traumatische Handrückenödem, Monatschr. f. Unfallh. **36**:289, 1929.

has taken on the character of spreading neuralgia, a hyperalgesia, which often defies segmental distribution. At this stage the condition is still amenable to treatment.

Finally, the atrophy progresses, involving the skin, muscles and bone, with ankylosis. Atrophy of the bone is now diffuse and indistinguishable from osteoporosis of other origin, such as that due to inactivity, senility, undernourishment and biliary fistula. The pain is now intractable. It has spread to the root of a limb, or even to the trunk. Patients so afflicted are frequently committed to insane asylums or commit suicide. Section of posterior roots or chordotomy has not been reported to give relief. Ablation of the sensory cortex has been suggested.

Because of the stress some authors have placed on osteoporosis, it must be emphasized that the diagnosis of Sudeck's atrophy can never be made on the basis of roentgenograms alone. The syndrome may be present in the absence of osteoporosis in the early stages, and, again, it may be subsiding when the changes in the bone are at their height. Nor does the pain follow the course of osteoporosis, for after adequate treatment it may rapidly subside but the osteoporosis persists for months. The value of roentgenograms lies in serial examinations. When coarse trabeculation occurs with evidence of recalcification, the peak of the syndrome has passed. I have not seen complete restitution of the osseous structure in my roentgenograms.

In previous communications [7] it was pointed out that in the history of patients with causalgic states major injuries to bones, joints, nerves or blood vessels are conspicuously absent. With few exceptions, the injuries occurred in the foot or hand, frequently around the ankle or wrist after a sprain or a minor fracture. The character of the initial trauma does not allow any prediction as to its late sequelae; this is obviously hard for some courts and compensation boards to understand.

In a series of plethysmographic studies, Miller and I [7b] showed that there is a persistently increased blood flow to the injured limb, which averages 30 per cent more than that to the uninjured, opposite extremity. We also found that heat increases this difference in blood flow between the two extremities and that cold does not decrease the flow to the extent that it does in the normal extremity.

It was also pointed out in these communications [7] that the mechanisms involved in all such causalgic states are identical. In this communication, I wish to report some observations bearing on the nature of this chronic, persistent vasodilatation.

VASODILATATION IN THE EXTREMITIES

One is accustomed to think of peripheral vasodilatation as myogenic or neurogenic. Direct application of heat and injection of papaverine, drugs of the theobromine group and nitrites act on the smooth muscle of arterioles and the venocapillary bed (fig. 1). One is also familiar with the vasodilatation which follows procaine block or surgical section of the sympathetic vasoconstrictor fibers (fig. 2). The vasodilatation associated with Sudeck's atrophy cannot be due to sympathetic efferent fibers, since sympathectomy not only does not abolish this type of vasodilatation but even increases it.[7] While it is generally assumed that

7. (*a*) de Takáts, G.: Reflex dystrophy of the Extremities, Arch. Surg. **34**:939 (May) 1937. (*b*) Miller, D. S., and de Takáts, G.: Posttraumatic Dystrophy of the Extremities, Surg., Gynec. & Obst. **75**:558, 1942. (*c*) de Takáts, G., and Miller, D. S.: Post-traumatic Dystrophy of the Extremities: A Chronic Vasodilator Mechanism, Arch. Surg. **46**:469 (April) 1943.

there are sympathetic cholinergic vasodilator fibers in man,[8] as in certain species of animals,[9] these fibers can hardly be responsible for the syndrome of Sudeck's atrophy, since vasodilatation persists after sympathectomy, although the pain is sometimes instantly relieved. In my experience, vasodilatation after sympathectomy has never caused burning causalgia; on the other hand, the vasodilatation to be studied here is of a steady, burning character associated with spreading

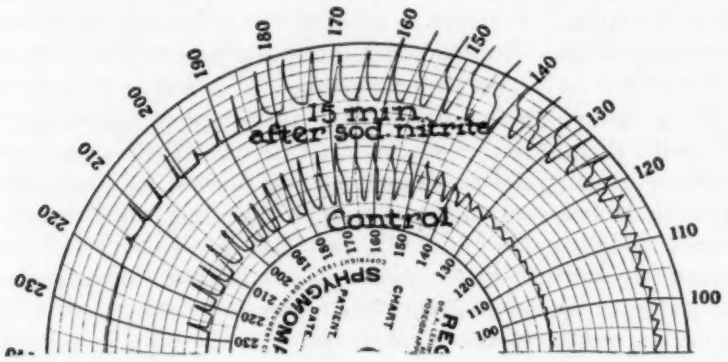

Fig. 1.—The oscillometric curve after intravenous injection of sodium nitrite. Note the shifting of increased pulse waves to the right, indicating the opening of the venocapillary bed. Compare the pulsations at a pressure of 140 mm. of mercury before and after injection of sodium nitrite. The extremity is warm and may flush. There is no pain. (Beck, W. C. and de Takáts, G.: *Am. Heart J.* **15**:158, 1938.)

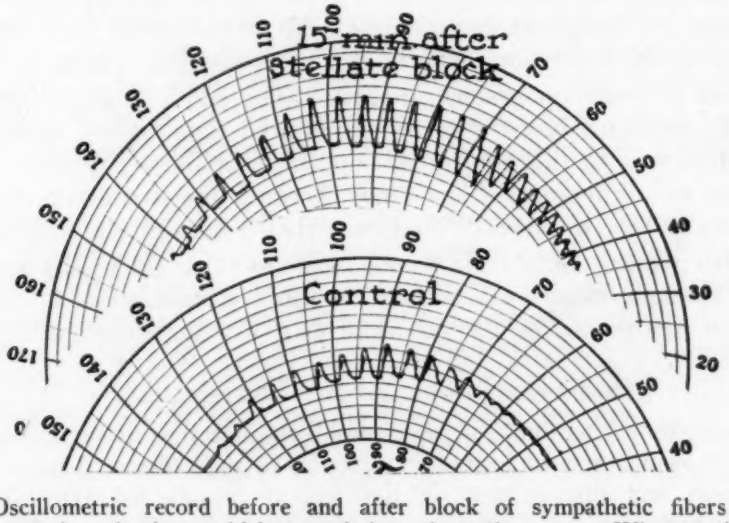

Fig. 2.—Oscillometric record before and after block of sympathetic fibers to the arm. Note the increase in pulsations, which extend throughout the curve. Whereas the pulse wave almost disappears at a pressure between 70 and 60 mm. of mercury before the injection, it is vigorous at the same level after injection. Peripheral resistance is lower. There is no pain.

neuralgia. This vasodilatation can be increased by a parasympathetic stimulant, such as prostigmine, whether the sympathetc fibers are present or not (fig. 3).

8. Lewis, T., and Pickering, G. W.: Vasodilatation in the Limbs in Response to Warming the Body, with Evidence of Sympathetic Vasodilator Nerves in Man, Heart **16**:33, 1931.

9. Burn, J. H.: Sympathetic Vasodilator Fibers—The Vasodilator Nerves, Physiol. Rev. **18**:137, 1938.

There may, of course, be cholinergic vasodilator fibers in the sympathetic outflow, and persuasive evidence that they are capillary dilators, producing flushing, has been accumulated by Hyndman and Wolkin.[10] These authors showed that the flushing produced by excessive heat or cold could not be produced after sympathectomy, even though it was present after section of the posterior roots. This observation would explain the relief from burning pain which occurs after sympathectomy in cases of Raynaud's phenomenon.

This type of chronic vasodilatation, accompanied by spreading neuralgia, can often be attributed to a recognizable lesion of a mixed peripheral nerve; however, not only the median and sciatic nerves but any peripheral nerve may be injured. A sprain often stretches the nerves around the wrist and ankle, and attention to the possibility of a partial nerve injury may elicit a segment of hyperesthesia. Since hyperesthesia is purely subjective, the elevation of cutaneous temperature or cutaneous resistance, closely following the sensory distribution of the same nerve, is frequently missed, and is significant.

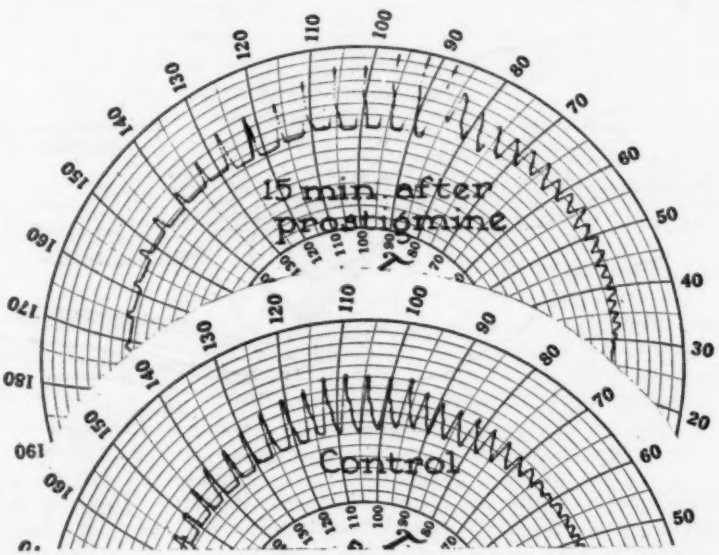

Fig. 3.—Oscillometric curves before and after injection of prostigmine methylsulfate in a sympathectomized limb. A sudden decrease in oscillations occurs at a pressure of 60 mm. of mercury before injection of prostigmine methylsulfate; after intramuscular injection of 1 cc., of a 1:2,000 solution there is a decided increase in the height of the pulse wave. Note, however, that the sudden decrease in pulsations occurs at a pressure of 80 mm. of mercury, 10 mm. higher.

A case in point is that of J. McM., who suffered a typical Colles fracture in falling on his wrist from a tank car. This was reduced in excellent position within twenty-four hours and immobilized in a posterior lycite splint by a competent orthopedic surgeon. The patient complained of numbness in the fingers from the start and a great deal of pain in the wrist. His fingers were said to have been numb when he left the hospital on the fourth day after injury. When he was admitted to my service, eight months later, there were no sensory or motor changes, but an area in the distribution of the median nerve over the hand and fingers was hot and dry. There was copious hyperhidrosis at the margins of this area. The oscillometric curves were higher for the injured side. There was no trigger point at the wrist,

10. Hyndman, O. R., and Wolkin, J.: The Autonomic Mechanism of Heat Conservation and Dissipation: Effects of Heating the Body, Am. Heart J. **22**:1, 1941; II. Effects of Cooling the Body, ibid. **23**:1, 1942.

but pain could be elicited on dorsiflexion. Because of persistent pain and only partial relief from repeated paravertebral injections, the median nerve of this patient was exposed. The perineurium was thickened and hyperemic. An organized hematoma was observed at the proximal edge of the carpal ligament.

The mechanism of such an injury is illustrated in figure 4. The median nerve can be caught between the proximal fragments of bone and the carpal ligament. Manipulations, the position of dorsiflexion for immobilization or a hematoma below the carpal ligament can bring about traumatic neuritis. The so-called wringer injuries of the wrist, without fracture or ruptured tendons may give rise to severe causalgia (2 cases in my series).

In another case seen with Dr. John T. Reynolds, burning pain and paresthesia were present on the dorsum of the right foot and the toes along the distribution of the superficial peroneal nerve. This, in turn, was caused by a large and painful fracture callus at the middle third of the tibia. The dorsum of the foot and the second, third and fourth toes were 2 degrees (C.) (3.6 degrees [F.]) warmer than the rest of the foot. The skin was dry, but no anesthesia was present. Since I have watched for these areas, I have found them to be not infrequent after painful sprains.

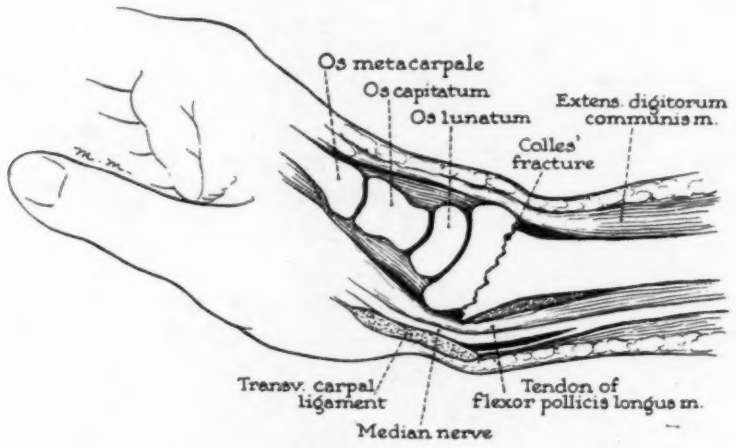

Fig. 4.—Median nerve injury in a case of Colles' fracture. This mechanism has been stressed and carefully studied by Abbott and Saunders (*Surg., Gynec. & Obst.* **57**:507, 1933).

These cases are cited to illustrate the importance of looking for cutaneous areas with increased temperature, and possibly decreased sweating, in the absence of objective sensory changes.

This segmental vasodilatation can be accentuated by production of reactive hyperemia in the limb after suprasystolic compression for five minutes. The painful vasodilatation, often accompanied by edema, can be aggravated by administration of prostigmine methylsulfate, as shown in figure 5. Such a phenomenon could be explained on the assumption that the cholinergic vasodilators are part of the posterior root system. The evidence for and against their existence and significance has been discussed by Fulton.[11] I have summarized in table 1 the accumulated data concerning these fibers. Apart from the evidence furnished by animal experiments,[12] the following clinical observations point to the existence

11. Fulton, J. H.: Physiology of Nervous System, New York, Oxford University Press, 1938.

12. Toennies, J. F.: Reflex Discharge from the Spinal Cord Over Dorsal Roots, J. Neurophysiol. **1**:378, 1938. Dole, V. P., and Morison, R. S.: A Note on the Question of Reflex Activation of Dorsal Root Dilators, Am. J. Physiol. **130**:30, 1940.

and clinical importance of the efferent fibers of the posterior roots: Stimulation of posterior roots produces segmental flushing of the skin. In fact, Foerster [13] used this method to map out sensory dermatomes. Attacks of vasodilatation may accompany tabetic crises, and the trophic changes in the bone are definitely associated with an increase in blood flow.[14] The herpes zoster produced by an irritative lesion of the posterior root ganglion can be made painless in the early stage by blocking of the paravertebral space distal to the ganglion. The causalgic pain following partial nerve injury may be stopped by block or section of the nerve distal to the injury.[15] But the most convincing clinical evidence comes from Lewis,[16] whose studies on cutaneous hyperalgesia are germane to this subject. Lewis postulated the secretion of a pain substance at the termination of nerve fibers which belong to the posterior root system. Since these fibers were neither sensory somatic nor sympathetic fibers, he named them nocifensor nerves. The

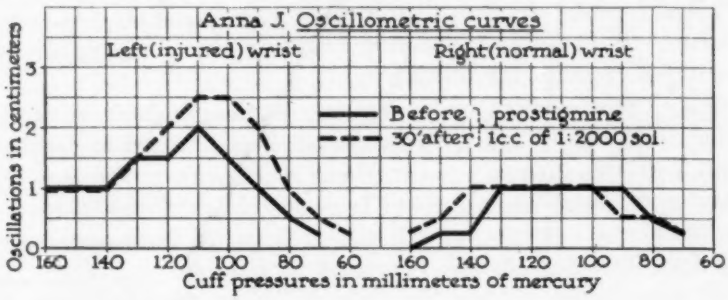

Fig. 5.—Oscillometric curves of a patient of Dr. B. F. Kilbourne who suffered from a painful wrist, with spreading neuralgia and increased oscillations, after a streetcar accident. The oscillations are higher on the injured side but fall abruptly after the peak pressure of 110 mm. of mercury. After injection of prostigmine methylsulfate the oscillations were greatly increased on the injured side and slightly shifted to the left on the opposite side. Pain and edema were aggravated on the affected side after the injection of prostigmine.

TABLE 1.—*Efferent Fibers of the Posterior Roots*

Year	Author	Evidence
1866	Loven.....	Flushing of ear on stimulation of posterior auricular nerve
1876	Stricker.....	Rise in temperature on stimulation of divided posterior root
1896	Werzloff.....	Fall in temperature on section of posterior roots
1901	Bayliss*.....	"Antidromic" vasodilatation on stimulation of cut end of sensory nerve
1918	Tinel.....	Relief from causalgic pain on section of sensory nerve distal, not proximal, to injury
1928	Foerster.....	Vasodilatation in corresponding dermatome by stimulation of cut end of posterior root in man
1935	Sheehan.....	Principle of forward conduction defined by "antidromic" conduction
1937	Lewis.....	"Nocifensor" system of nerves in man
1938	Toennies.....	Centrifugal reflex discharge in cut sensory nerves

* Bayliss, W. M.: The Vasomotor System, London, Longmans, Green & Co., 1923.

13. Foerster, O.: Ueber die Vasodilatatoren in den peripheren Nerven und hinteren Rückenmarkswurzeln beim Menschen, Deutsche Ztschr. f. Nervenh. **107**:41, 1928.

14. Exaltier, P.: Des troubles sympathiques associés aux ostéoorthopathies syringomyéliques, et tabétiques, Thesis, Lyon, 1925. Bascourret, H.: Les troubles vasculaires dans le tabes, Thesis, Paris, 1927. Cornil, L., and Paillas, J.: Considerations anatomo-pathologiques sur l'orthopathie des tabétiques, Rev. neurol. **1**:525, 1933.

15. Tinel, J.: Causalgie du nerf médian, par blessure à la partie moyenne du bras; insuffisance de la sympathectomie périartérielle; guérison par la section et suture du nerf au poignet, Rev. neurol. **25**:79, 1918.

16. Lewis, T.: Experiments Relating to Cutaneous Hyperalgesia and the Spread Through Somatic Nerves, Clin. Sc. **2**:373, 1936.

histologic background for the existence of naked terminals in the subepidermal and epidermal layers has been supplied by Woollard.[17]

The nature of this chronic vasodilatation and the abolition of its painful, throbbing character by sympathetic block or by arterial compression suggest another important point. Under ordinary conditions, capillary pressure is kept within relatively narrow limits, whether or not there are arterial hypertension and arteriolar vasoconstriction.[18] The pulsating, throbbing pain associated with Sudeck's atrophy, its rapid abolition by suprasystolic compression and its aggravation by venous stasis certainly suggest capillary hypertension. This concept would also explain the frequent presence of edema, first periarticular and later diffuse and spreading. Capillary microscopy often reveals dilated, pulsating capillaries in the early stage. The trauma producing Sudeck's atrophy seems to activate both vasoconstrictor and vasodilator fibers, with dominance of the vasodilators. This must lead to increase in capillary pressure and stimulation of the sensory receptors, including the arteriovenous shunts. The throbbing, burning pain of causalgia is so closely simulated by the pain and vasomotor phenomena seen with glomus tumors that the latter may be readily overlooked.[7b]

Any treatment, then, which will decrease capillary pressure and capillary dilatation should bring about relief. Immersion in cold water is frequently practiced by patients with this disease. Sympathetic block with procaine, with acceleration of the blood flow, opens the arterioles but constricts the capillaries. The relief obtained from sympathetic block is striking, in spite of increased vasodilatation. In this connection, attention should be called to the observations of Gesell and his associates,[20] who suggested that the rate of disappearance of acetylcholine is dependent on the acidity of the tissue. With reference to the present problem, reflex vasoconstriction, which is invariably present after trauma, inhibits the destruction of acetylcholine; after sympathetic block there is a shift to the alkaline side, so that the acetylcholine is rapidly destroyed. Of course, there is no proof that acetylcholine is the pain substance of Sudeck's atrophy, but it is certain that sympathetic block may relieve postherpetic neuralgia; in fact, Hyndman [21] expressed the belief that the pain in postherpetic neuralgia is mediated through sympathetic fibers.

TREATMENT

In treatment of this frequent, but often unrecognized, lesion, I have made extensive use of injections into sympathetic nerves and of sympathectomies. Table 2 shows the procedures used and the results obtained. Gradually, the following method has been evolved:

For the early, mild form, sufficient immobilization and daily injections of a 1 per cent solution of procaine hydrochloride into the injured area are almost specific. The important factor is sufficiently early recognition of the syndrome. When the neuralgia has spread beyond the site of the injury, and this may take from ten to thirty days, paravertebral injections of procaine should be given, and repeated as the relief from pain wears off. These injections may have to be given daily, or once a week may be sufficient; in favorable cases the duration of their

17. Woollard, H. H.: Intra-Epidermal Nerve Endings, J. Anat. **71**:54, 1936.

18. Eichna, L. W., and Wilkins, R. W.: Capillary Blood Pressure in Induced Vasoconstriction, J. Clin. Investigation **21**:697, 1942.

19. Footnote deleted.

20. Gesell, R.; Brassfield, C. R., and Hamilton, H. A.: An Acid Neurohumoral Mechanism of Nerve-Cell Activation, Am. J. Physiol. **136**:604, 1942.

21. Hyndman, O. R.: Postherpetic Neuralgia in the Distribution of Cranial Nerves, Arch. Neurol. & Psychiat. **42**:224 (Aug.) 1939.

effect is increasingly longer. When sympathetic block promptly abolishes the symptoms but they recur with undiminished intensity after a few hours or days, sympathetic ganglionectomy should be immediately undertaken. For the upper extremity, the infiltration or removal of the stellate ganglion is undesirable; the second and third thoracic ganglia are far more important. This is true even of the procaine injections. I have repeatedly failed to relieve this painful syndrome with block of the stellate ganglion from the front when a posterior injection into the second and third ganglia was successful. For the lower extremity, removal or infiltration of the second and third lumbar ganglia is sufficient. It should be pointed out that if a preliminary procaine block fails to relieve the symptoms even for a short time, sympathectomy will also fail. In the present material, the reasons for such resistance to treatment have been found to be as follows:

1. In a group of cases of the late stage of the disease, contracture, ankylosis and a period of inactivity had produced so much functional impairment that orthopedic measures were necessary. There is, however, relief from pain in some cases of this type.

TABLE 2.—*Results of Treatment in Cases of Sudeck's Atrophy*

Type of Treatment	No. of Cases	Recovery *		
		Complete	Partial	None
Cast; splint; physical therapy	8	1	3	4
Repeated procaine block	1	..	1	..
Repeated sympathetic block	8	7	1	..
Periarterial sympathectomy	3	2	1	..
Perivenous stripping	2	2	..	..
Sympathetic ganglionectomy	8	5	3	..
No treatment	6	..	2	4
Total	36	17	11	8

* By complete recovery is implied restoration of function; by partial recovery, cessation of pain with limitation of function, and by no recovery, stationary or deteriorating physical or mental status.

2. In cases of the late severe form, the spreading neuralgia is intractable; it may involve the shoulder, the thoracic wall and the opposite limb. The patient has a severe psychoneurosis, either because of his original makeup or because of continued, unrelieved pain. Such a patient truly acts as if his hypothalamus had been continuously stimulated; he perspires; the heart is rapid, and he shows profound anxiety. One man, a patient of Dr. Carl Rinder, showed muscular twitchings, shivering and clonus, comparable to the running or clawing movements of Ranson's [22] cats. As Grinker and Serota [23] showed, the electric pattern of the resting hypothalamus can be changed by stimulation with weak currents, with excitation of both the hypothalamus and the cortex; with a certain amount of strong current, cortical dominance over the hypothalamus is lost, with resulting impulsive, unconscious actions—a functional decortication. The observations of these authors on animals and on human subjects strengthen the assumption that emotions influence intellectual processes through the mechanism of the hypothalamus' driving, and finally inhibiting, the cortex.

That the fear of inadequate compensation for the sustained injury, the anxiety of permanent injury to a part, aggravates the syndrome in many patients needs no emphasis. In our work, in cooperation with our neuropsychiatrists, my associates

22. Ranson, S. W.: Some Functions of the Hypothalamus, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 92.

23. Grinker, R. R., and Serota, H.: Studies on Corticohypothalamic Relations in the Cat and Man, J. Neurophysiol. **1**:573, 1938.

and I have felt that most of these injuries, unless promptly relieved, are followed or accompanied by "states of mind," for which adequate psychotherapy is just as important as local therapy.

Consideration of how such corticohypothalamic reactions can be corrected is not within the scope of this paper. The point must be made that early relief of this continuous, intractable pain and the proper reassurance of the patient may prevent the late complications. At this late stage neither section of the posterior roots nor chordotomy has done any good.[23a] Section of the spinothalamic tract in the medulla oblongata [24] and mesencephalic tractotomy [25] may seem desperate measures. However, patients suffering from this condition become drug addicts; their personality changes are obvious, and some have committed suicide. Such an operation seems indicated if psychiatric help has failed.

SUMMARY

A group of 36 cases has been studied in which phenomena of spreading neuralgia and chronic vasodilatation were exhibited. The initial injury in most cases is slight but may involve partial mild injury to posterior root fibers. The early interruption of vasomotor disturbances and the block of the sensory barrage of higher centers readily abort the syndrome. The late stage will not yield to such peripheral interruptions and requires central intervention by psychiatric, and possibly by surgical, methods. It is suggested that cholinergic vasodilator fibers are activated in this syndrome.

122 South Michigan Boulevard.

23a. White, J. L., and Smithwick, R. H.: The Autonomic Nervous System: Anatomy, Physiology, and Surgical Application, ed. 2, New York, The Macmillan Company, 1941.

24. Schwartz, H. G., and O'Leary, J. L.: Section of the Spinothalamic Tract in the Medulla with Observations on the Pathway of Pain, Surgery **9**:183, 1941.

25. Walker, A. E.: Mesencephalic Tractotomy: A Method for the Relief of Unilateral Intractable Pain, Arch. Surg. **44**:953 (May) 1942.

MENINGIOMA OF THIRTY YEARS' DURATION

REPORT OF A CASE

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The age and rate of growth of primary tumors arising from the meninges can seldom, if ever, be accurately determined. To judge the approximate age of neoplasms in other parts of the body, one usually depends on the duration of symptoms produced. Unfortunately, this criterion cannot be applied to intracranial tumors, particularly meningiomas. A lesion arising in the epileptogenic zone may manifest its presence early, whereas one involving a "silent area" of the brain may grow for a long time, often reaching an enormous size before its presence is suspected.

The age of secondary, or recurrent, tumors, on the other hand, can be accurately determined when the onset of growth, i. e., the time of the first operation, is known. The rate of growth of these recurrent lesions is variable and depends on the pathologic variety of the tumor, its location and the extent of the operative and postoperative treatment. Of all intracranial neoplasms, the meningioma is probably the most slow growing. Bailey and Bucy's [1] classification of meningeal tumors includes nine distinct pathologic types. Cushing and Eisenhardt [2] have described numerous subdivisions of these types.

It is suggested that a possible correlation exists between the pathologic type of a tumor and its rate of growth, the meningiomas which resemble the embryonic structure of the meninges being classified as malignant and tending to grow more rapidly. This type of meningioma was described early by Craig,[3] and more recently by Turner, Craig and Kernohan.[4]

As to the location of the neoplasm in the skull, Cushing and Eisenhardt [2] found in a series of 313 cases of meningioma that the meningioma en plaque, arising from the pterion bone of the sphenoid ridge had the longest clinical history, an observation suggesting that the growth of tumors in this location is slower. Nine of their 16 patients with this tumor had had symptoms for an average of over nine years. The operative and postoperative treatment will be discussed later.

It is the purpose of this communication to report a case of recurrent meningioma which was known to have been growing for nearly thirty years. It is our belief that this is the "oldest" meningioma yet to be reported. A careful search of the literature has failed to reveal a similar case in which the age of the tumor was definitely known. In Cushing's series of patients with meningiomas many have reached the thirty year postoperative period, but, as far as is known, none has

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1. Bailey, P., and Bucy, P. C.: Origin and Nature of Meningeal Tumors, Am. J. Cancer **15**:15-54 (Jan.) 1931.

2. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behaviour, Life History, and Surgical End Results, Springfield, Ill., Charles C Thomas, Publisher, 1938, pp. 36 and 70.

3. Craig, W. M.: Malignant Intracranial Endotheliomata, Surg., Gynec. & Obst. **45**:760-768 (Dec.) 1927.

4. Turner, O. A.; Craig, W. M., and Kernohan, J. W.: Malignant Meningiomas: Clinical and Pathologic Study, Surgery **11**:81-100 (Jan.) 1942.

had recurrence of the tumor. In a patient operated on twenty-five years ago slowly spreading hyperostosis of the skull has developed at the site of the original tumor, but the patient is well and free from symptoms.[5]

REPORT OF CASE

Convulsions at age of 17 years. First operation November 1911, with removal of globoid tumor and right frontal bone. Recovery. Patient well until 1937, when convulsions returned with increasing frequency. Progressive change in personality. Encephalogram, made in 1939, showed large intracranial neoplasm in right frontal region. Second operation,[6] November 1939: removal of globoid tumor, weighing 267.7 Gm. Final diagnosis: Intracranial neoplasm (meningioma) with psychosis. Complete recovery, with subsequent mental deterioration.

L. W., a man aged 49, a Caucasian, was admitted Oct. 7, 1939, on voluntary application, to the Territorial Hospital, Kaneohe, Hawaii, with a diagnosis of psychosis, chronic alcoholism and major convulsions.

Past History (obtained subsequently in detail from the patient).—About 1907, when the patient was 16 years of age, he first began to have headaches and to notice gradual enlargement of the right side of the forehead. During the next two years the right eye became more prominent. He began to have convulsions, which increased in frequency. His family noticed a change in his personality. Although previously of a mild disposition, he had become quick tempered and irritable. In November 1911, at the age of 21, he was admitted to the Stanford-Lane Hospital, San Francisco, with almost continuous left-sided jacksonian convulsions. There was conspicuous bulging of the right side of the forehead, with downward and forward protrusion of the right eye. Biopsy of material obtained at the first operation, on Dec. 7, 1911, was reported by Dr. W. Ophlus as follows:[7]

"The surgical specimen consisted of a piece of tissue from the orbital surface of the roof of the orbit, which was firmly attached to the bone, and a piece of the necrotic bone above the supraorbital ridge. The duration of growth had been three to five years.

"Histologic examination showed a tumor composed of dense bundles of large spindle cells, which in places had connective tissue fibrils, between which were a moderate number of blood vessels. In parts of the tumor the bundles of cells were so sharply separated that on cross section some appeared like alveoli filled with polygonal cells. The dividing line between the groups of cells and the adjoining fibrillar tissue, however, was not sharp. The tumor resembled certain neoplasms of the dura mater. In the necrotic piece of bone tumor tissue seemed to have filled the medullary spaces."

The diagnosis was alveolar sarcoma of the roof of the orbit.

With this diagnosis of "sarcoma," two radical cranial operations were performed by Dr. S. O. Beasley[8] and Dr. E. C. Sewall. The hospital record of these operations could not be found. A personal communication from Dr. Sewall, however, informed us of the extent of the procedures.

"On December 9, a bone flap was elevated over the right eye and a large tumor, approximately 5 cm. in diameter and fairly round, was removed from a smooth nest in the frontal lobe, from which it peeled easily and cleanly. Then, on December 29, the thickened bone, which included the entire supraorbital ridge, the roof of the orbit, the frontal bone flap, the right eye and the entire contents of the right orbit were resected."

The second pathologic report (Dr. Ophlus) read as follows:

"Back of the eyeball, in bone from the roof of the orbit and the region of the frontal sinus was a typical tumor. The growth showed the same structure as that described before except that in some places it is very fibrous and did not show an alveolar arrangement."

The diagnosis was alveolar sarcoma of the dura mater.

After the operation, according to the patient's statement, he received high voltage roentgen therapy over the operative site twice a week for five months!

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5. Eisenhardt, L.: Long Postoperative Survivals in Cases of Intracranial Tumor, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:390-416, 1937; personal communication to the authors.

6. Although the exact time from the first to the last operation was twenty-eight years, it is assumed that the portion of tumor not removed at the first operation, from which the present lesion developed, had been growing for three to five years, so that it was of thirty years' duration or more.

7. This report was obtained through Dr. David A. Wood, of the department of pathology, Stanford University Hospitals.

8. Dr. Beasley was killed in action in World War I, in 1918.

Interval History.—The patient made an excellent recovery from this extensive operation. His convulsions ceased, and his mental impairment cleared in a short time. He was well until 1917 (five years later), when his convulsions returned. He was placed in the hospital and another operation performed, in which "adhesions were broken up between the dura and the skull" (quoted from Dr. Sewall's letter). He had no further trouble after this.

In May 1912 the patient was employed by the California State Department of Agriculture, where he received training as an entomologist. He came to Hawaii in 1920 as inspector for the United States Department of Agriculture, a responsible position which he held up to his admission to the hospital in 1939. He used a microscope daily with his one eye. He became a thirty-second degree Mason, was active in social and civic affairs and was well liked by all who knew him. The death of his wife, in 1937, was thought by his friends to have been the cause of a decided mental change which he began to show. His convulsions began again, though, except for one or two attacks in 1925, he had been free of them since 1917. He became a habitual drinker, and excessive use of alcohol precipitated a convulsion. He lost interest in his lodge, his occupation and himself. Because of his heavy drinking, he entered the Territorial Hospital on voluntary application on Oct. 7, 1939.

Present History.—On his admission to the Territorial Hospital the patient was alert, cooperative, apparently rational and properly oriented. His mood was cheerful and pleasant

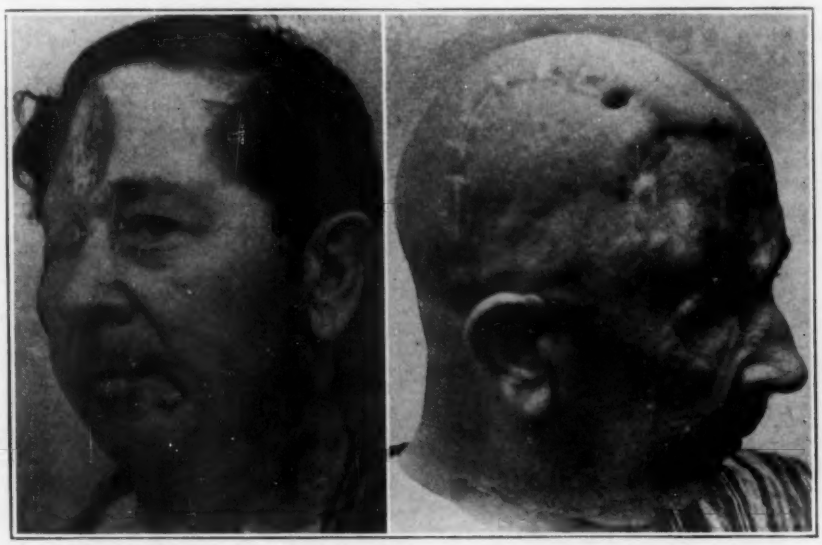

Fig. 1.—Preoperative photograph of the patient, showing extent of the radical removal of the skull and right eye at the first operation, in 1911. The slight bulging of the decompression area gave little indication of the enormous tumor beneath.

most of the time, although he was occasionally irritable. No defects of memory for remote or recent events were found. Retention and calculation were normal. The presence of hallucinations was denied. His stream of thought was spontaneous and coherent. Judgment and insight were adequate except in respect to his mental condition, which he felt was normal. His chief complaint was his convulsions. He admitted using alcohol to excess. Subsequent observation showed him to be irritable, quick tempered, talkative, uncooperative and filthy. He expectorated on the floor and often urinated on the wall while lying in bed. He refused to take a bath. He took little interest in his surroundings and remained on his bed most of the time, smoking incessantly.

Physical Examination.—The patient was tall and well developed. The bone over the right half of the forehead and the supraorbital ridge had been removed, with a resultant defect in the skull which extended from the midline to just in front of the ear and as far back as the hair line (fig. 1). The skin over this defect was a thin, atrophic scar, covered with greasy scales, the result of the extensive course of high voltage roentgen therapy which had been given after the first operation. This area protruded slightly, but did not pulsate. The right eye was missing. There was no other physical defect. The heart, lungs and abdomen were not remarkable. The blood pressure was 118 systolic and 70 diastolic, and the pulse rate was 68 per minute.

Neurologic Examination.—The results were essentially negative. The left optic disk was slightly pale but otherwise normal; there was no evidence of papilledema. The pupil reacted well to light and in accommodation. There was slight weakness of the left lower part of the face. Sensory and motor examinations gave completely normal results. The deep tendon reflexes were sluggish but equal on the two sides. There was no pathologic toe sign.

Laboratory Data.—The Wassermann reactions of the blood and spinal fluid were negative. Repeated urinalyses gave normal results. The blood counts were all within normal limits. Roentgenograms of the skull disclosed, in addition to the bony defect, ragged, "moth-eaten" areas at the outer angle of the right orbit and the temporal bone. There was a small area of calcification (1 by 0.5 cm.) near the midline, deep in the right frontal region.

An encephalogram was performed on November 23. The roentgenograms revealed a large, space-occupying lesion which displaced the right frontal lobe of the brain. The conspicuous deformity and downward depression of the frontal horn of the lateral ventricle clearly demonstrated the size and extent of the tumor mass (fig. 2).

Diagnosis.—The diagnosis was a large recurrent intracranial neoplasm, probably a meningioma.

Operation.—The first stage was performed at the Queen's Hospital, Honolulu, on December 4. With procaine anesthesia, a large scalp flap was turned down over the old operative defect. The thin, atrophic skin was dissected with difficulty from the underlying dura mater, to which it was firmly attached. A large amount of soft, vascular, mushy bone

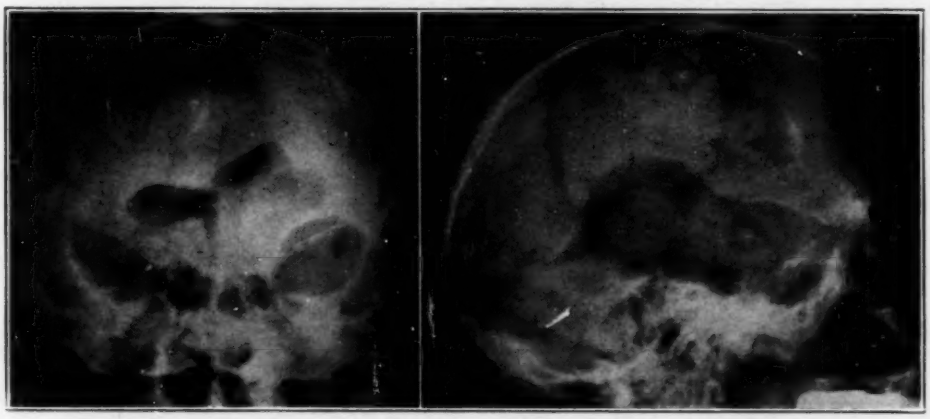

Fig. 2.—Encephalogram, demonstrating the conspicuous deformity of the right frontal horn of the lateral ventricle by the large globoid tumor. A small calcified area is seen in the midline, near the center of the tumor.

was rongeured from the edge of the defect. Two weeks later with the patient under anesthesia induced with avertin with amylene hydrate, the scalp flap was reopened. With considerable difficulty, because of its vascularity, a large, soft, nodular, fleshy tumor was removed with the aid of the electric cautery. The tumor separated freely from the brain beneath. It was removed in its entirety with the overlying dura mater, to which it was firmly attached. A large piece of fascia lata from the patient's thigh was used to close the defect in the dura mater.

Pathologic Report.—The tumor tissue removed (fig. 3) weighed 267.7 Gm. The largest mass after fixation measured 10 by 7 by 4 cm.; it comprised about two thirds of the total neoplasm. The dura mater attached to the tumor reached a maximum thickness of 3 mm. and contained calcium. The microscopic diagnosis was meningioma type I, variant 3, according to the classification of Cushing and Eisenhardt.[2] The tumor cells were chiefly spindle shaped and arranged in interlacing bundles, with a tendency to whorl formation (fig. 4). No psammoma bodies or collagen masses were seen. Connective tissue stains demonstrated the absence of fibroblastic elements among the tumor cells; these fibroblasts were limited to the blood vessels. The latter were not so numerous microscopically as was expected from the gross consistency of the tumor. No mitotic figures were present. The alveolar spaces of the soft, mushy bone were filled with tumor tissue.

Subsequent Course.—The postoperative course was stormy, owing to several serious complications. The thin scalp flap was accidentally perforated at the second operation, and a

cerebrospinal fluid fistula resulted. On the fifth postoperative day, a stiff neck developed; the temperature rose to 103 F., and cloudy fluid drained from the hole in the skin. The fluid contained a pure culture of Staphylococcus aureus haemolyticus. The patient was given sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), 1 Gm. every four hours. The

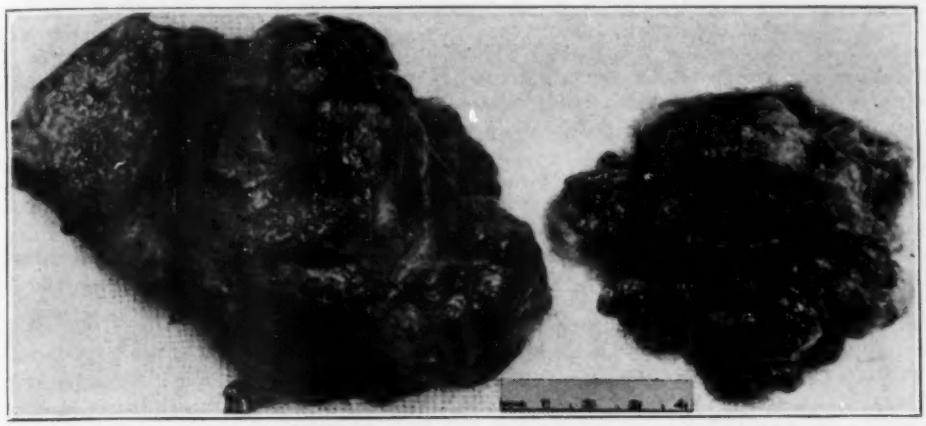

Fig. 3.—Photograph of meningioma, weighing 267.7 Gm. (× ¼). The larger mass (left) was removed in one piece; the smaller mass, composed of pieces, was resected with the electric loop.

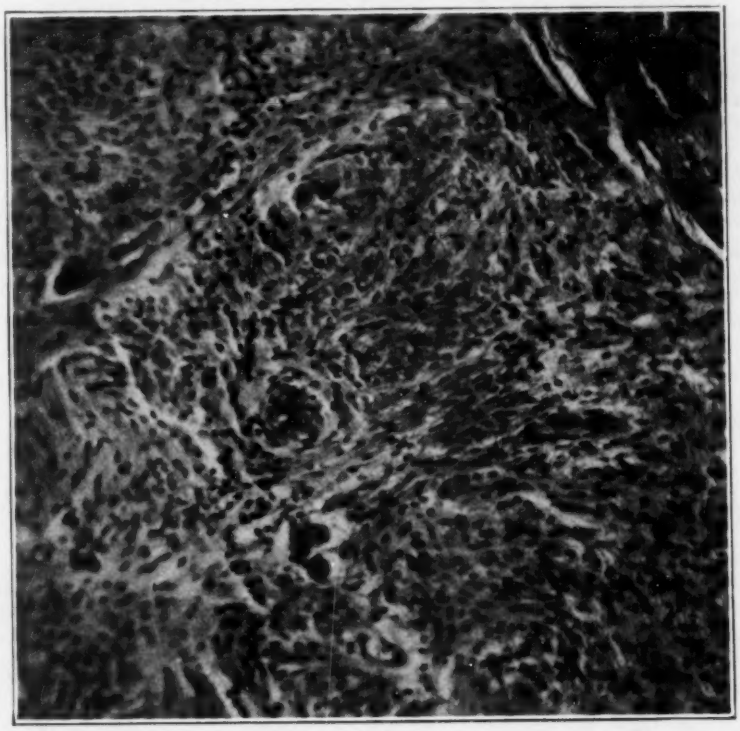

Fig. 4.—Photomicrograph, showing characteristic structure of the meningioma (× 150).

center of the scalp flap around the perforation became gangrenous, and an area of skin, 3 by 4 cm., and the underlying fascia lata sloughed out, with exposure of the brain beneath. Cerebrospinal fluid and pus drained from this area for about three weeks. With the administration of sulfapyridine by mouth, which was continued in the dose previously stated for sixteen days, the infection gradually subsided, and healthy granulation tissue appeared .

About two weeks after operation the patient suddenly went into shock, the pulse rate mounting to 140 a minute and the blood pressure falling to 90 systolic and 70 diastolic. He became unconscious. The nurse had reported a large dark bowel movement shortly before. Examination revealed several blood clots filling the rectum, which when removed were followed by bright red blood. The patient's red blood cell count fell to 2,900,000 and the hemoglobin concentration to 48 per cent. A transfusion of 500 cc. of whole blood was given. The first proctoscopic examination, made by Dr. C. M. Burgess, failed to reveal the source of the bleeding. The rectum was packed. Three days later the patient had another massive rectal hemorrhage of over 300 cc. of bright red blood and again went into shock. Proctoscopic examination this time disclosed a medium-sized arterial bleeder in the center of a small ulcer on the anterior wall of the rectum, 3 inches (7.6 cm.) above the anus. The artery was tied, and the condition did not recur.

About six weeks after operation (one month after the rectal hemorrhage and three weeks after administration of the sulfapyridine had been discontinued) jaundice developed; over a period of ten days, the icterus index gradually increased from an initial level of 50 to one of 75. The van den Bergh reaction was biphasic, with 3 mg. of bilirubin per hundred cubic centimeters. The jaundice then gradually decreased. The icterus index three weeks later was 25. The cause of the jaundice was not determined.

The patient was in Queen's Hospital eight weeks and was then transferred to the Territorial Hospital for convalescence. During this entire time he showed no interest in his surroundings. He would lie staring at the ceiling for hours at a time. He never spoke unless spoken to, and then only in single words. At no time was there weakness of his left extremities; the weakness of the left side of the face, however, was more pronounced than before the operation. He was incontinent of urine most of the time. Because of the limited blood supply of the atrophic skin, the large ulcer in the scalp flap failed to epithelize. After about ten weeks, small, superficial pinch grafts of skin were taken from the thigh and placed on the healthy granulating bed. The area promptly healed over.

Follow-Up Observations.—The patient was kept in the Territorial Hospital until May 18, 1940, about six months after operation. During his period of convalescence his mental reaction gradually returned to normal, so that at the time of his discharge it was the opinion of the attending psychiatrist (R. D. K.) that he had recovered sufficiently to return to society and his employment and take up where he had left off eight months before. He returned to his former occupation of entomologist and plant inspector. His employer informed us that the patient's efficiency and capability in his work was about as good as before he became ill. This efficiency in his work and stability of character continued for over a year. His thirst for alcohol then returned, and he began drinking again, which he has continued to do up to the present. In the past year he has gradually lapsed into a mental state similar to his immediate preoperative condition. He is irresponsible and cannot be depended on in his work. He has few friends. He has an occasional convulsive attack, associated with his alcoholism, in spite of receiving large doses of anticonvulsant drugs.

COMMENT

As already stated, the factors which influenced the rate of growth of this tumor were its type and location and the operative and postoperative treatment. The original tumor in this case was probably a meningioma en plaque, arising from the sphenoid bone. Dr. Cushing's statistics show that tumors in this location grow more slowly and have longer clinical histories than any other intracranial meningioma. Likewise, a tumor located far forward in the frontal lobe is often symptomless for a long time and may not manifest its presence until it has reached a considerable size.

Whether the release of pressure by removal of a large area of the skull over an intracranial neoplasm will influence the rate of growth of the tumor is difficult to say. Offhand, one might expect a tumor to be retarded in its growth when the confines of the intracranial space are limited by an intact skull. Conversely, with a large decompression—plently of space into which the tumor can expand—one would expect its growth to be more rapid. In our case, however, the size of a cranial decompression appeared to exert no influence whatsoever on the rate of growth of the tumor, for even with an extensive defect in the overlying skull, the tumor grew slowly for nearly thirty years. The large decompression,

on the other hand, was probably indirectly responsible for the age of the tumor because it prevented the symptoms of intracranial pressure which would otherwise have developed long before.

At this point we feel justified in adding a word of praise for the surgeons—Dr. Sewall and Dr. Beasley—who performed the first operation on this patient in 1911. At that early date neurosurgery as a specialty was unknown; elective operations on the brain were seldom attempted, and when they were their mortality was so high as to discourage even the bravest of surgeons. These pioneer surgeons are to be praised for their courage in undertaking and their skill in accomplishing such radical and extensive removal of the tissues of the head invaded by tumor.

It has long been known that roentgen therapy is ineffective in slowing the growth of primary meningiomas.[9] But it seems possible that a recurrent tumor might be retarded in its growth by the effect of roentgen radiation on surrounding tissues. In this case, could not the roentgen rays, producing sclerosis and fibrosis of the dura, blood vessels and bone, have increased the resistance of these tissues to the invading neoplasm? It is possible that these deep tissues, and perhaps even the brain itself, may have been severely damaged by the extensive course of high voltage roentgen therapy which was given after the first operation. It has been shown by Alpers and Pancoast[10] and by O'Connell and Brunschwig[11] that roentgen rays may produce degenerative changes in even normal tissues of the central nervous system.

The postoperative complications, which included meningitis, local infection of the wound, intestinal hemorrhage, obstructive jaundice and alteration in the mental state, also deserve further discussion.

The postoperative infection at the site of the operation was attributed to the atrophic, devitalized condition of the scalp. We were aware of the hazard of having to operate through this devitalized skin, but there was no alternative. There is no doubt that use of sulfapyridine was partially, if not wholly, responsible for the patient's recovery from this infection. The extensive local infection at the site of the operation and the generalized meningitis would almost certainly have proved fatal without it.

The cause of the massive rectal hemorrhage which threatened the patient's life ten days after the operation was not determined. The small ulcer noted in the rectum had apparently oozed for about four days. A larger vessel then opened, with acute loss of blood, which caused the patient to go into shock. It is possible that this erosion of the intestinal wall was directly attributable to the disturbance of the functions of the frontal lobe by the operation. As has been shown by Watts,[12] Watts and Fulton[13] and Mettler and his co-workers,[14] bilateral experimental

9. Bailey, P.: Results of Roentgen Therapy on Brain Tumors, Am. J. Roentgenol. **13**:48-53 (Jan.) 1925.

10. Alpers, B. J., and Pancoast, H. K.: Effect of Irradiation on Normal and Neoplastic Brain Tissue, Am. J. Cancer **17**:2-24 (Jan.) 1933.

11. O'Connell, J. E. A., and Brunschwig, A.: Observations on Roentgen Treatment of Intracranial Gliomata with Especial Reference to Effects of Irradiation upon Surrounding Brain, Brain **60**:230-258 (June) 1937.

12. Watts, J. W.: Influence of the Cerebral Cortex on Gastro-Intestinal Movements, J. A. M. A. **104**:355-357 (Feb. 2) 1935.

13. Watts, J. W., and Fulton, J. F.: Intussusception: Relation of Cerebral Cortex to Intestinal Motility in Monkey, New England J. Med. **210**:883-896 (April 26) 1934.

14. Mettler, F. A.; Spindler, J.; Mettler, C. C., and Combs, J. D.: Disturbances of Gastro-Intestinal Function After Localized Ablations of Cerebral Cortex, Arch. Surg. **32**:618-623 (April) 1936.

removal of the frontal lobe in monkeys and chimpanzees frequently results in erosions of the gastrointestinal tract. The possibility of gastrointestinal hemorrhage following injury of or operation on the frontal lobe should be kept in mind. If routine examinations of the stools are made in cases of damage to the frontal lobe, loss of blood from the intestinal tract can be recognized early and treated before the patient's life is endangered.

The cause of the jaundice which appeared six weeks after the operation was also not determined. The condition may possibly have been hemolytic jaundice, but it did not appear for one month after the rectal hemorrhage. It may have been "infectious jaundice" with acute hepatitis, secondary to infection of the wound. Or the sulfapyridine administered may have damaged the liver. The sulfonamide compounds exist in the blood in both a "free" and a "combined" form—the latter with acetyl radicals. It has been shown that long after the free drug has been excreted, the compound form may remain in the blood. It may be that the jaundice of this patient was due to the toxic effect on the liver of the "combined" sulfapyridine still in the blood stream three weeks after the drug was stopped. Another possibility, since the jaundice was of the obstructive type, is the presence of another lesion in the mucous membrane of the duodenum, similar to the bleeding ulcer seen in the colon. Such a lesion near the ampulla of Vater, with tissue reaction and edema about it, might temporarily obstruct the outlet of the common bile duct. We have never seen or heard of jaundice occurring as a direct complication of an intracranial operation.

The patient's mental condition has been progressively downhill during the three years since his operation. For the first eighteen months after he returned to his work his output was good—"almost as good as before the operation," according to his employer. However, he has shown more and more the irresponsible, shiftless, lackadaisical personality characteristic of patients who have had the frontal lobes of the brain removed or injured.[15] Both frontal lobes of this patient's brain were undoubtedly extensively damaged. The delay in the development of his mental deterioration may be attributed to formation of scar tissue at the site of the operation, to the effects of the alcohol he consumed or to both.

SUMMARY

The case of a patient with a recurrent intracranial meningioma of the right frontal lobe of thirty years' duration is described. The factors thought responsible for the slow growth of the tumor are discussed. These include the type and location of the neoplasms, the extensive, radical removal of the bone at the first operation and the postoperative roentgen therapy.

An interesting series of complications which followed the removal of the recurrent tumor included gangrene of the wound, meningitis, acute hemorrhage from the rectum, found to be due to erosion of the mucosa of the colon, obstructive jaundice and gradual mental deterioration. The cause of these complications and their relation to the intracranial operation are discussed.

388 Young Building, Honolulu, Territory of Hawaii.
Territorial Hospital, Kaneohe, Oahu, Territory of Hawaii.

15. Strauss, I., and Keschner, M.: Mental Symptoms in Cases of Tumor of Frontal Lobe, Arch. Neurol. & Psychiat. **33**:986-1007 (May) 1935.

MULTIPLE MENINGIOMAS

REMOVAL OF FOUR TUMORS FROM REGION OF THE FORAMEN MAGNUM AND UPPER CERVICAL REGION OF THE CORD

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The following observation on multiple meningiomas was deemed worthy of report because of its rarity and its unusual surgical aspect. According to Echols,[1] who recently reviewed the literature and added an observation of his own, 53 cases of multiple meningiomas have been recorded hitherto.

Multiple meningiomas follow no particular pattern of localization; in fact, the tumors may occur wherever the arachnoid cell clusters described by Schmidt [2] and Aoyagi and Kyuno [3] are situated. In most of the cases of multiple meningiomas reported the tumors were intracranial or intracranial and spinal; there were only few instances of multiple spinal meningiomas. The incidence of multiple meningiomas is certainly small as compared with the frequency of single tumors; yet the figures of different authors vary considerably in this respect. Thus, Cushing and Eisenhardt [4] found 3 cases of multiple meningiomas in a series of 313 cases of intracranial and spinal meningiomas, and Frazier and Alpers [5] observed 1 instance in a series of 75 cases; yet Horrax [6] found 4 cases in a group of 60 cases of meningioma of the brain.

In the past, the occurrence of multiple meningiomas was looked on as a mere pathologic curiosity, but the advent of the neurosurgical era has brought an increasing number of reports describing the successful removal of these lesions (Heuer and Dandy [7]; Dandy [8]; Raaf and Craig [9]; Woltman and Love [10]; Cushing and Eisenhardt [4]; Echols [1]). The following personal observation may serve as an illustration.

From the Department of Surgery, University of Michigan.

1. Echols, D. H.: Multiple Meningiomas, Arch. Neurol. & Psychiat. **46**:440-443 (Sept.) 1941.

2. Schmidt, M. B.: Ueber die Pacchionischen Granulationen und ihr Verhalten zu den Sarkomen und Psammomen der Dura, Virchows Arch. f. path. Anat. **170**:429-464, 1902.

3. Aoyagi, F., and Kyuno, K.: Ueber die endothelialen Zellzapfen der Dura mater cerebri und ihre Lokalisation in derselben, nebst ihrer Beziehung zur Geschwülstbildung in der Dura mater, Neurol. Tokio **11**:1-12, 1912.

4. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C Thomas, Publisher, 1938.

5. Frazier, C. H., and Alpers, B. J.: Meningeal Fibroblastomas of the Cerebrum, Arch. Neurol. & Psychiat. **29**:935-989 (May) 1933.

6. Horrax, G.: Meningiomas of the Brain, Arch. Neurol. & Psychiat. **41**:140-157 (Jan.) 1939.

7. Heuer, G. J., and Dandy, W. E.: A Report of Twenty Cases of Brain Tumor, Bull. Johns Hopkins Hosp. **27**:224-237 (Aug.) 1916.

8. Dandy, W. E., in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1940, vol. 12, p. 520.

9. Raaf, J. E., and Craig, W. M.: Multiple Meningiomas, Arch. Surg. **31**:601-606 (Oct.) 1935.

10. Woltman, H. W., and Love, J. G.: Multiple Intracranial Meningiomas with Extension to the External Auditory Canal: Successful Removal; Presentation of Case, Proc. Staff Meet., Mayo Clin. **10**:497-501 (Aug. 7) 1935.

REPORT OF A CASE

E. McC., a 46 year old housewife, was referred to the neurologic outpatient clinic of the University of Michigan Hospital by Dr. H. R. Mooi, Union City, Mich., Sept. 13, 1941.

History.—For ten years the patient had complained of frequent suboccipital headache, occurring mostly when she was in the recumbent position. Approximately two years prior to admission the suboccipital pains became more frequent and severe. At the same time the patient noticed progressive weakness of both legs, especially the left, and staggering gait. The weakness gradually progressed and affected also the arms, until the patient became practically paralyzed in all four extremities. Seven months prior to admission, however, gradual spontaneous improvement took place. At the time of her visit to the clinic she was able to walk again with assistance, the left leg being stronger than the right. A year prior to admission the patient experienced a sensation of coldness and numbness in the right arm and hand, occasionally accompanied by aching and burning pains. At the same time she had difficulty in initiating urination and was troubled with precipitate micturition and occasional fecal incontinence. Furthermore, she described recent episodes of diplopia, lasting two months.

Examination.—General physical examination revealed no significant changes, especially no cutaneous manifestations of Recklinghausen's disease. Neurologic examination disclosed mild nuchal rigidity. There were fine oscillatory nystagmus with the eyes in the primary position and coarse horizontal nystagmus on lateral gaze to the right and left; otherwise the cranial nerves were normal. The extremities showed generalized loss of muscle substance but no localized atrophy. There were spastic paresis of all four limbs, with greater involvement of the right side, and mild ataxia of the extremities. The deep reflexes of the arms and legs were hyperactive, and the signs of Hoffmann, Babinski and Rossolimo were present bilaterally. The abdominal reflexes were abolished. Slight tactile hypesthesia and hypalgesia were demonstrable from the second cervical to the fourth dorsal dermatome, especially on the right side; all other sensory modalities were intact. The patient walked, with some assistance, in a spastic-ataxic manner, and the Romberg sign was positive.

Roentgenographic examination revealed a normal cervical portion of the spine and no limitation of diaphragmatic movements.

Lumbar puncture yielded clear, colorless fluid, under an initial pressure of 170 mm. There was partial manometric block, with a sluggish response to jugular compression. The spinal fluid contained 4 lymphocytes per cubic millimeter, and the Pandy reaction was positive. The total protein content was 183 mg. per hundred cubic centimeters; the Kahn reaction was negative; the colloidal gold curve was 0011000000, and the mastic curve was 111100.

Diagnosis.—The diagnosis was probable tumor of the spinal cord at the level of the second to the fourth cervical segment. No conclusion was reached as to whether the lesion was intramedullary or extramedullary. Exploratory high cervical laminectomy was advised, but the patient declined to undergo operation at that time.

Second Admission.—The patient was not heard of again until July 1, 1942, when she was admitted as an inpatient to the neurosurgical service of the University of Michigan Hospital, nine and one-half months after her previous visit. She then stated that the weakness of her limbs had progressed considerably during the past five months and that she now was unable to walk. Furthermore, she complained of severe pain in the back of her neck.

Second Examination.—The head and neck were held in a stiff, guarded position. There were nuchal rigidity on attempted passive movement and pain referred to the suboccipital region. Slight paresis of the right sixth cranial nerve and horizontal nystagmus to the right were present. The ocular fundi, visual fields, hearing and vestibular responses and all other functions of the cranial nerves were normal. While laryngoscopic examination revealed no involvement of the vagus nerve, the pulse rate was rapid, averaging 100 a minute. The spastic tetraparesis of the extremities was far more pronounced than it had been on the previous examination, so that the patient could hardly move the right arm and leg at all. Also, the sensory changes had increased considerably. Definite diminution of all forms of superficial sensation (touch, pain and temperature) could be demonstrated below the level of distribution of the trigeminal nerve bilaterally.

Diagnosis.—The diagnostic impression at this time was tumor of the spinal cord in the high cervical region, at the level of or near the foramen magnum. The probability of an extramedullary tumor was considered slightly greater than that of an intramedullary lesion.

Operation.—On July 2, 1943, with the patient under anesthesia induced with solution of tribromethanol U. S. P., supplemented by intratracheal administration of ether (Dr. C. F. List), the suboccipital bone and the upper four cervical vertebrae were exposed by means of a vertical midline incision. A small suboccipital decompression was made, and the posterior rim

of the foramen magnum was removed, the procedure being carried out farther laterally on the right side, since here the bone appeared pathologically thinned. The spinous processes and the posterior laminas of the four upper cervical vertebrae were also removed. The rather tight cerebellar dura was opened in a stellate manner, and this incision was joined with a vertical midline incision in the cervical part of the dura. The posterior cistern was observed to be practically effaced, and the exposed part of the cervical portion of the cord bulged posteriorly to a pronounced degree. There was a nodular, gray-white tumor, the size of a large almond, to the right of the first and second cervical segments, displacing the cord to the left. Below this level the spinal cord showed a definite hump, possibly an indication of a mass in front of it (fig. 1 *A*). The exposed tumor had the macroscopic characteristics of a firm meningioma. It was covered with arachnoid and was attached to the posterolateral portion of the dura, posterior to the slip of the denticulate ligament and near the exit of the second cervical posterior root, which it displaced anteriorly. The tumor could be easily removed *in toto,* after division and coagulation of its attachment, a deep groove being left in the posterolateral aspect of the cord. The second cervical nerve root was not injured. Next, a second tumor, the size of a small plum, was brought into view, a little rostral to the one just removed (fig. 1 *A* and *B*). The lower pole of this tumor, which was evidently also a meningioma, extended from beneath the right cerebellar tonsil and the lateral margin of the foramen magnum slightly downward into the spinal canal. Its main mass lay hidden by the cerebellum in the lower part of the right cerebellopontile angle and anterolateral to the medulla oblongata. Because of the size of the lesion and its precarious location, piecemeal removal appeared advisable. At first the broad attachment of the growth was removed from the lateral rim of the foramen magnum, together with infiltrated dura and some suspicious-looking bone. Then the upper pole could be mobilized at the region of the jugular foramen, where it was gently dissected from the lower rootlets of the vagus nerve, without injuring them. Finally, the medial and anterior portions of the growth were dislodged from beneath the medulla and cautiously separated from the spinal accessory nerve and the vertebral artery, to which the tumor was adherent. After extirpation of the second tumor, a review of the operative field disclosed a third meningioma, which had previously been hidden as a result of the rotation and marked displacement of the upper part of the spinal cord to the left side. This third tumor, the size of a large bean, was situated to the left of the second cervical segment and was partially covered by the left second posterior cervical nerve root (fig. 1 *C*). It could easily be removed *in toto,* after division of its lateral dural attachment and of the second posterior cervical root. No sooner had this nodule been removed than a fourth meningioma was brought into view, which was the size of a small olive and lay anteriorly and anterolaterally, to the left of the second and third cervical segments (fig. 1 *D*). This tumor caused the posterior bulge of the cord, previously noted. It had an anterolateral dural attachment between the second and the third anterior cervical nerve root on the left side and displaced the ascending rootlets of the spinal accessory nerve posteriorly. In order to avoid trauma to the compressed cord, this tumor was removed piecemeal and its attachment coagulated. Unfortunately, the left spinal accessory nerve was injured during the procedure. On investigation of the left cerebellomedullary angle, a suspicious nubbin was seen extending from the region of the left vertebral artery to the base of the cerebellar tonsil. It was not definitely ascertained whether this was a fifth tumor or a prominent vertebral artery covered by arachnoid. More than four hours having been spent on the removal of four benign tumors at a critical location, it was considered unwise to continue the operation and to attempt removal of other tumors which might still be present (fig. 2). The wisdom of this decision was borne out by the postoperative course, as the patient undoubtedly would have died had the operation been more extensive. Consequently, the spinal dura was closed with silk, but the cerebellar dura had to be left open. The muscles were sutured in three layers with steel wire, and the subcutaneous layer was sutured with catgut and the skin with silk.

Histologic Examination.—The four tumors which were removed were identical in structure; all were typical psammomatous meningiomas, with considerable hyalinization.

Postoperative Course.—On the first and second days the patient's condition was good; there was already slight improvement of the paresis of the right arm and leg, but bilateral paralysis of the sternocleidomastoid muscle was noted. On the fourth postoperative day, however, her temperature rose to 103 F. She showed respiratory embarrassment, dysarthria and increasing tetraplegia. Her condition continued gradually to grow worse, until on the seventh postoperative day it was desperate. She was semiconscious, confused and cyanotic, with a temperature of 107 F. and a respiratory rate of 28 a minute. The tetraplegia had become complete. Since it was not known whether this state was due to postoperative bleeding or to medullary edema with thrombosis, it was decided to reopen the incision. This was done with local anesthesia on July 9. There was no evidence of postoperative bleeding. The

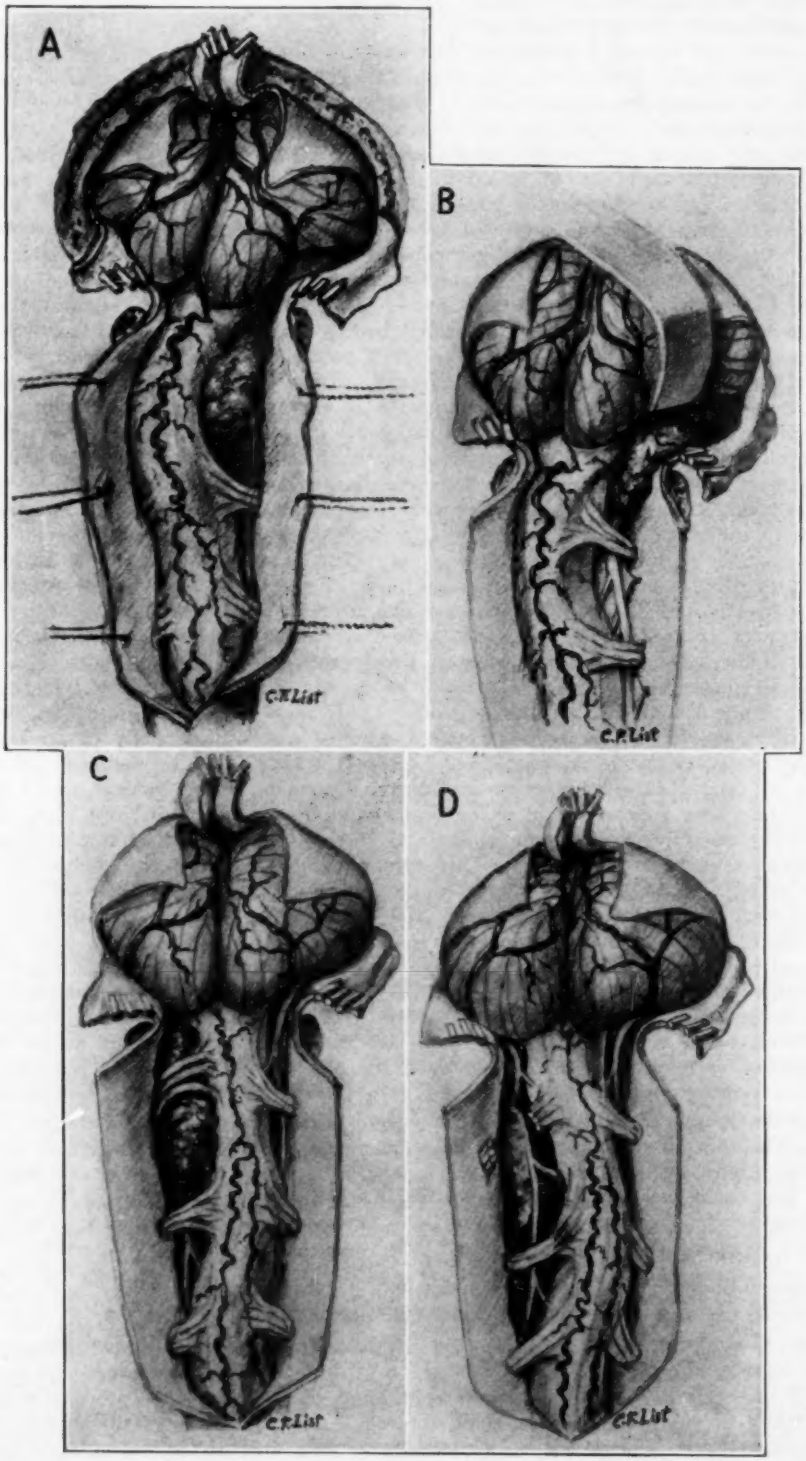

Figure 1

(See legend on opposite page)

exposed cerebellum, medulla and spinal cord were a little swollen, with engorged vessels. The incision was closed as before. After operation, the patient was kept in an oxygen tent. Her general condition began to improve slowly. On the eleventh postoperative day the temperature became normal. She was still confused; speech was bulbar in type; swallowing was difficult, and the tetraparesis had only slightly receded. From that time recovery was rapid. The temperature remained normal. The incision had healed by first intention, and the pareses of the extremities were definitely less, the left leg remaining the weakest of the extremities. The bulbar signs had completely subsided by the seventeenth postoperative day. On the twenty-sixth day the patient was up in a wheel chair. She had gained further strength in her extremities, but she experienced difficulty in holding her head upright because of the weakness of the muscles of the neck. The inlying catheter, which had been necessary ever since her operation, was removed. With physical therapy, she began to walk, and finally she was discharged on August 13, forty-six days after operation.

Further Course.—The patient was readmitted a month later, September 14, with the complaint of severe pain and stiffness of the neck and pain in the left shoulder. Reexamination showed painful muscular spasm of the neck and mild periarthritis of the left shoulder. She could move all her extremities well, although with diminished strength. Both legs and the right arm showed pronounced ataxia of cerebellar type. The deep reflexes were hyperactive,

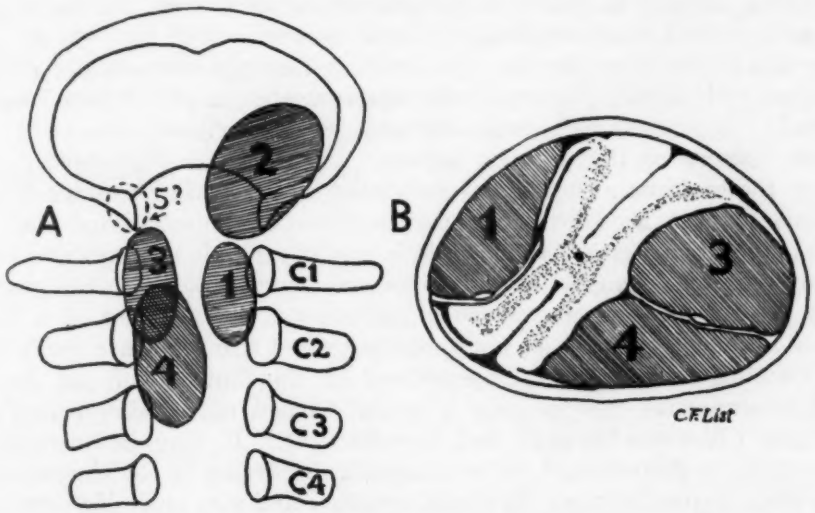

Fig. 2.—Diagrammatic sketches showing the approximate size and location of the four, or five (?), meningiomas encountered at operation. *A*, relation of the tumors to the foramen magnum and the cervical portion of the spine; *B*, cross section of the spinal cord at the level of the second cervical segment, showing relation of the tumors to the cord and the meninges.

and pathologic toe signs were elicited. The sensory changes were confined to decrease in pain and temperature sensation in the left lower extremity.

Explanation of Figure 1

Drawings illustrating the observations at operation in a case of multiple meningiomas. (*A*) The first meningioma is exposed to the right of the first and second cervical segments. The lower pole of the second meningioma is just visible lateral to the right cerebellar tonsil. The still concealed third and fourth tumors cause a posterior bulge of the spinal cord at the level of the second and third cervical segments. (*B*) The first tumor has been removed. The second meningioma, extending from the first cervical segment to the right cerebellopontile angle, is exposed. (*C*) The third meningioma is exposed to the left of the second cervical segment; it is covered by the second posterior cervical nerve root. (*D*) After removal of the third tumor (the second posterior cervical root has been divided), the fourth meningioma is exposed, lying anterior and to the left of the second and third cervical segments and covered by the root of the spinal accessory nerve.

New roentgenograms of the cervical portion of the spine revealed no dislocation of the cervical vertebrae at the site of the previous laminectomy. The patient's difficulties cleared after application of a Forrester collar and with continued physical therapy. At the time of discharge, on August 30, she was able to walk with slight support.

Follow-Up Examination (March 25, 1943).—When the patient was last seen, eight months after operation, she stated that she could walk with slight support and was able to do her own housework. Examination showed that the strength of all extremities had improved remarkably. She was able to walk fairly well by herself and to hold her head upright without support, but there were still considerable atrophy and paresis of the left sterenocleidomastoid and of both trapezius muscles. The sensory changes had practically disappeared.

When last heard of, one year after operation, the patient reported further improvement. She is now able to walk and to perform her household duties without difficulty.

COMMENT

Survey of the literature reveals that the term "multiple meningiomas" is not, and perhaps cannot be, sharply defined. According to Cushing's [4] suggestion, "multiple meningiomas" should designate several discrete tumors, but something less than a diffusion of them. If the neoplastic nodules are numerous and coalesce, the condition should be called meningiomatosis, or diffuse meningioma(tosis). Undoubtedly, there exist transitional forms between these two types. Another difficulty has arisen from the fact that multiple meningiomas are not infrequently encountered with Recklinghausen's neurofibromatosis. In this disease, the growths are usually associated wth neurofibromas and sometimes also with gliomas and other tumors of the nervous system. Cushing and Eisenhardt [4] classified separately the multiple meningiomas associated with Recklinghausen's disease and the lesions without accompanying manifestations of neurofibromatosis. Such a distinction appears arbitrary, as shown by a case of multiple meningiomas which I [11] previously reported. In this particular instance, multiple basilar meningiomas were the only tumors affecting the nervous system; yet the presence of a few small cutaneous fibromas and café au lait spots suggested that this case really belonged to the Recklinghausen type. Observations of this kind favor the theory that multiple meningiomas may be only a special variant of Recklinghausen's neurofibromatosis (Worster-Drought and associates [12]). It may be mentioned here that, according to Kernohan,[13] the meningiomas occurring in Recklinghausen's disease are often atypical in their histologic structure and may resemble neurofibroma; at any rate, there is evidence that (multiple) meningioma and neurofibroma are genetically related neoplasms. The case reported here permits no conclusive answer to the various problems of classification and pathogenesis; however, in the absence of signs of neurofibromatosis, the lesions must simply be labeled "multiple meningiomas."

The clinical diagnosis of multiple meningiomas as a rule is difficult. If the tumors are small and situated in silent areas, neither the presence of a neoplasm nor its multiple character may even be suspected. In other instances, the localizing diagnosis of a neoplasm is correctly made, but the multiplicity of the lesions is not anticipated. This error appears excusable if, as in my observation, the tumor nodules are crowded in a relatively small area and hence the clinical symptoms can be explained by a single large lesion. Yet there are cases on record in which the clinical evidence in itself clearly indicated multiple localization. In

11. List, C. E.: Multiple Meningiome der Schädelbasis (zugleich ein Beitrag zur Differentialdiagnose der Kleinhirnbrückenwinkeltumoren), Nervenarzt **6**:566-574, 1933.

12. Worster-Drought, C.; Dickson, W. E. C., and McMenemey, W. H.: A Multiple Meningeal and Perineural Tumor with Analogous Changes in the Glia and Ependyma (Neurofibroblastomatosis), Brain **60**:85-117 (March) 1937.

13. Kernohan, J. W.: Tumors of the Spinal Cord, Arch. Path. **32**:843-883 (Nov.) 1941.

other instances the presence of several tumors was revealed by roentgenographic examination. Finally, the multiplicity of the lesions became evident in some cases only after one of the tumors had been removed and residual or new symptoms permitted a clear recognition of the condition.

This leads to a discussion of the surgical management of multple meningiomas. One might say that failure to diagnose the condition in this case may have been a blessing in disguise, because had the cautious neurosurgeon anticipated the presence of multiple tumors, he would perhaps have hesitated to take a chance on what later proved to be a highly satisfactory operation. The technical difficulties of removing multiple meningiomas are often less than those of the extirpation of a large solitary neoplasm, since multiple nodules usually are small and can be dealt with individually in succession, with relative ease. On the other hand, the presence of concealed lesions, not exposed in the operative field, may lead to unexpected and serious complications during or after the operation; hence the operative risk must be considered high. Even though multiple meningiomas have been removed successfully, the possibility always remains that not all the tumors have been found and that trouble may develop eventually at other locations. This course of events has been well described by Cushing, who had an opportunity to follow his patients over a number of years. In spite of the guarded surgical prognosis of multiple meningiomas, an attempt at removal appears always worth while, as shown by the result obtained in the case reported here.

University of Michigan Medical School.

RECURRENT AUTONOMIC PHENOMENA ASSOCIATED WITH EXACERBATIONS OF POSTENCEPHALITIC PARKINSONISM

REPORT OF A CASE

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The unhappy manifestations of epidemic encephalitis continue to provide the opportunity for provocative excursions into the physiology of the human central nervous system. This report is concerned with a patient who presented features of recurrent autonomic release associated with exacerbations of chronic postencephalitic parkinsonism. The episodic nature of the phenomenon and the occurrence of mutism in the presence of unimpaired cerebration are additional features of interest.

REPORT OF CASE

History.—Charged with housebreaking, a Negro aged 32 was transferred to Gallinger Municipal Hospital from the district jail on Sept. 25, 1933 for mental observation. He had previously sought admission to that hospital in August 1931, complaining of stiffness of his left arm. At that time the facies were masklike, and he held his left upper extremity flexed and dragged his left leg while walking. His movements were slow, and some cogwheel rigidity was observed in the left upper extremity. The Kahn reaction of the blood was 2 plus. Mental examination at that time revealed nothing significant. Three days later the patient left the hospital with the diagnosis of postencephalitic parkinsonian syndrome, without psychosis.

After his first admission, the patient had been unable to resume work. His left arm grew weaker. At times he was unable to sleep and rambled around the neighborhood. On these occasions there developed a desire to see nude women, and he would peep in at apartment house windows. Simultaneously he became impotent and lost normal sexual desire. During 1932 the patient had noticed difficulty in initiating conversation, and a sense of stiffness in the face. Oculogyric crises, recurring about once in two weeks and lasting about ten minutes, began to appear. Speech became dull and monotonous. Although realizing that his behavior was abnormal, and feeling guilty about his peculiarities, he at times followed women to their homes, waited until he thought they were alone and in bed and then entered the house and attempted to touch the sleeping victim on the thigh, fleeing as soon as she awoke and discovered him. After the last episode of this nature, the patient was apprehended by the police and, after a few days in the district jail, was sent to the Gallinger Municipal Hospital. The results of mental and physical examinations at this time were identical with those on the previous admission. On Oct. 27, 1933 he was transferred to Saint Elizabeths Hospital.

The patient was born in Washington, D. C., in 1901. His birth and childhood were not considered unusual. He did rather well at school and left after his second year in high school. For many years he had no difficulty in keeping employed, and he worked industriously, although he never held a position of any responsibility. There were arrests for "speeding," "fornication" and "investigation."

In childhood the patient had whooping cough and mumps. At the age of 16 an attack of chickenpox caused him to leave school, and a few months later he had a "touch of pneumonia." He had a chancre at the age of 17, but no antisyphilitic therapy was given. The family history was noncontributory.

At Saint Elizabeths Hospital the patient's behavior was exemplary. He not only conducted himself well but assisted in the care of the more helpless patients. Speech was monotonous, without inflection, and he was slow in initiating motion or speech. His conversation, however, was relevant and coherent. He appeared mildly euphoric. Aside from a feeling that his peculiar sexual proclivities were recognized by others, no abnormal mental trends were

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noted. He was precisely oriented. Memory was excellent. General information was unusually full. Calculations were rapid and accurate. Appreciation of his situation and condition was good.

Examination.—The patient was well nourished and appeared to be comfortable. The face was oily, and the palm of the left hand was more moist than that of the right one. The heart and lungs were normal; the blood pressure was 140 systolic and 110 diastolic. The teeth were in poor condition. In walking he dragged the left leg and did not swing the left arm. The head was held immobile. The face was masklike, with the mouth constantly somewhat open, and he occasionally drooled a little. The pupils were round and equal but exhibited scarcely perceptible contraction both to light and to distant vision. The face was unexpressive, and its response to both mimetic and voluntary innervation was impaired. The tongue was tremulous, but otherwise the lower cranial nerves functioned well. Sensation was intact. The abdominal and cremasteric reflexes were active and equal on the two sides. The left upper extremity was hypertonic, and the movements were slow, with cogwheel rigidity. In addition, this extremity occasionally exhibited a fine tremor. The deep reflexes of the lower extremities were active and equal on the two sides. Plantar stimulation induced active flexion bilaterally. Serologic tests for syphilis gave negative reactions.

Course of Illness.—The patient adjusted well to the ward routine and, although somewhat restive at first, became resigned to spending the rest of his life in the institution. On one occasion, when given some privileges, he wandered away from the service to a distant part of the hospital grounds and fell asleep. Another time he was picked up at some distance from the hospital, obviously confused and not attempting to escape. He was suspected of making homosexual advances to other patients, but the suspicions were never confirmed.

Physically, he improved somewhat on administration of 0.6 mg. of scopolamine hydrobromide two to four times daily. During July 1934 it was noted that he perspired excessively without provocation. His intake of food and water was considered remarkably large. In September of that year he appeared stuporous at intervals. Despite his bradykinesia, he played baseball enthusiastically and, although he was not very proficient, displayed surprising agility. During the first two weeks of 1935 occasional stupor and diurnal sleepiness were observed. In the spring of 1935 oculogyric crises recurred at fortnightly intervals. Several months later attacks of mutism ("the patient was hardly able to answer a single question") concurrent with spells of stupor, lasting about twenty-four hours, were observed. About a year later a fairly constant monthly incidence of these attacks became obvious. On June 13, 1936 the patient had one of his spells of mutism, this time associated with fairly profuse diaphoresis. On this occasion the temperature rose to 100 F., the pulse rate to 140 and the respiratory rate to 30 a minute. After a hypodermic injection of 0.6 mg. of atropine sulfate, the patient began to recover. One month later tremulousness and diaphoresis, as well as mutism, appeared with the oculogyric crises and recurred with steadily increasing severity and frequency, which late in 1939 was recorded as once or twice a week. On July 21, 1940 scopolamine was discontinued, and the next day a preparation of belladonna alkaloids was prescribed. On July 23 the patient was observed to perspire profusely. This episode lasted about three days, during which the temperature rose to 100.6 F. and the pulse to 130 a minute. Although the patient claimed that he felt more comfortable while receiving the belladonna alkaloids, the frequency of the spells was not changed.

In December 1942 the patient seemed alert and well informed. He discussed the war at length and intelligently. Spontaneous speech was meager, and his responses to questions were slow and measured, being delivered in a dull, monotonous voice. They were, however, coherent, relevant and logical. He claimed that he was contented with his situation. No abnormal mental trends could be elicited. He was precisely oriented. Calculations were promptly and accurately performed. Memory was excellent. He repeated 7 digits forward and 5 in reverse. He had some insight into his physical and mental condition. Masking of the facies was evident. The skin was greasy, especially over the face. The mouth, through which the patient breathed with a slight noise, stood open. The heart and lungs were normal, and the blood pressure was 110 systolic and 90 diastolic. The pupils responded neither to light nor to distant vision. Convergence was poor, the patient fixing with each eye separately and alternately. Facial movements were limited, more on voluntary than on mimetic innervation. The lower cranial nerves were normal. The left upper extremity was held in flexion at all joints, which resisted change. The cogwheel phenomenon was observed in both left extremities. The skin of the left hand was hot and moist, and the hand was contracted in flexion. There was a lesser degree of rigidity, with the cogwheel phenomenon, in both right extremities. A fine, rapid tremor was observed in both left extremities. The left leg was dragged in walking. The deep reflexes were underactive on the left side and normally active on the right. The cremasteric reflexes were weak bilaterally. There was no Hoffmann or Babinski sign. Sensation was intact. When

the patient was standing in the Romberg position, with the eyes shut, he tended to fall backward, but invariably moved his feet back in time to prevent falling. Under hypnosis, he was definitely, but only superficially, influenced.

While the patient was under continuous treatment with the preparation of belladonna alkaloids, attacks continued at a rate of one or two a week, each lasting one to three days. When medication was discontinued, on Dec. 24, 1942, an attack followed within two days (fig. 1). First there was increase in the amplitude of the tremor on the left side, and even the right extremities became visibly tremulous. It became more difficult for the patient to

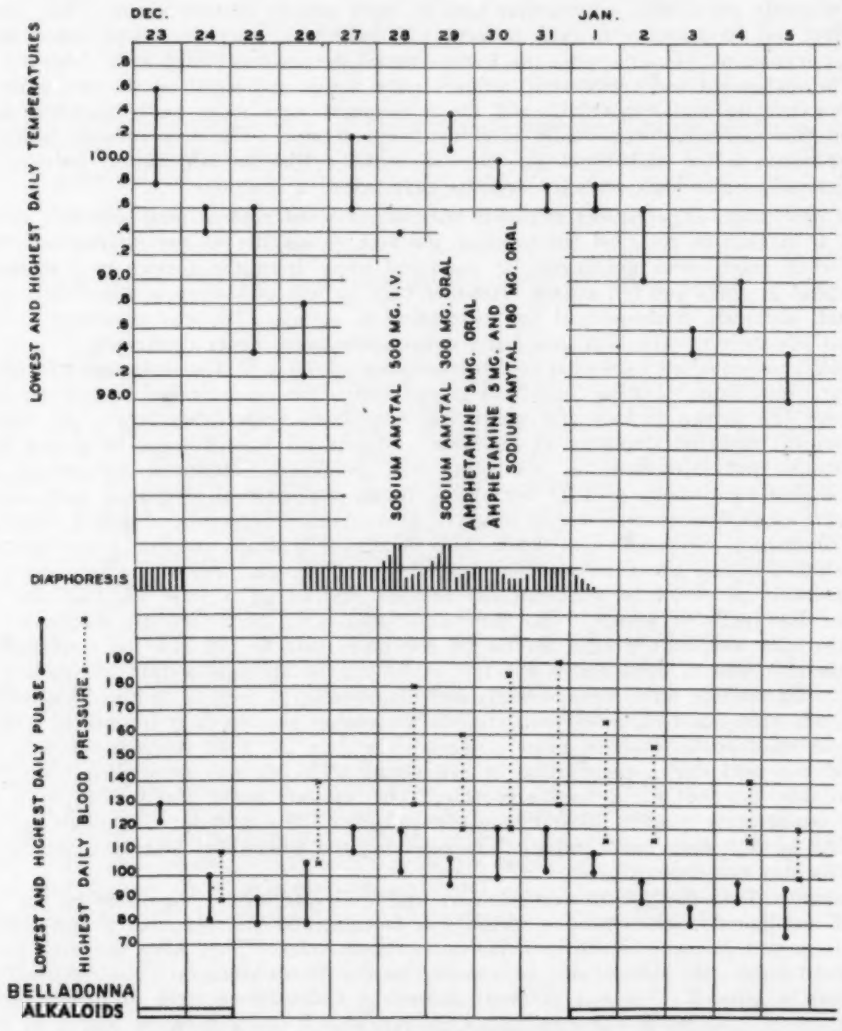

Fig. 1.—Variations in vital functions in an attack induced by withdrawal of a preparation of belladonna alkaloids immediately after recession of a spontaneous attack.

move about, and this akinesia gradually extended to involve the speech mechanism, so that he became mute. At first this was partial, so that he spoke only on being urged, and in a barely audible voice, one or two words at a time. The akinesia was associated with rigidity, so that true flexibilitas cerea existed. Visible response was limited to slow withdrawal to strongly noxious stimuli only. He was, however, able to control his ocular movements. The last phenomenon to appear was diaphoresis, with other obviously autonomic manifestations. The temperature was maintained close to 100 F., the pulse rate between 110 and 120 and the respiratory rate at about 25 a minute. The blood pressure, which in the interval state was recorded at 110 systolic and 90 diastolic, rose to 190 systolic and 130 diastolic. At times while in this condition the patient became incontinent. Because of the profuse diaphoresis

there was severe oliguria. The degree of diaphoresis was difficult to measure; however, after the face and forehead were dried, beads of perspiration stood out and coalesced to a running stream within three minutes (fig. 2). The skin was warm, and the lips were swollen. After intravenous administration of 0.5 Gm. of sodium amytal the patient was able to speak a few words, though barely audibly. There was certainly not the dramatic change that occurs in patients with schizophrenic catatonia. At the same time, he began to cough and raise mucus. The blood pressure, temperature and pulse rate dropped and the perspiration diminished, all slightly but definitely. The symptoms recurred in about six hours. An oral dose of sodium amytal had similar, but less pronounced, effects. Five milligrams of amphetamine sulfate only intensified the tremor, although there was perhaps less difficulty in speaking. Because the patient was becoming progressively weaker, treatment with the preparation of belladonna alkaloids was resumed on Jan. 1, 1943, and the phenomena almost immediately began to recede, in the inverse order of their appearance, so that by January 3 he seemed to have returned to

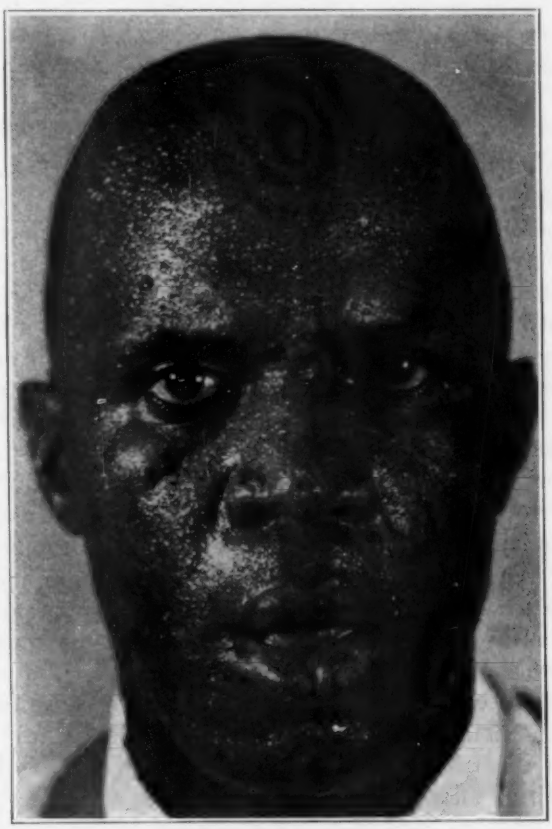

Fig. 2.—Diaphoresis, swelling of the lips, protrusion of the tongue and panting respiration less than twenty-four hours after withdrawal of medication (May 20, 1943).

the interval state. He was able to discuss the events of the past few days, which he had apparently observed accurately. He claimed that he had wanted to answer the questions put to him and had attempted to do so, but for some reason, which was obscure to him, he was unable to make the necessary movements.

During January amphetamine sulfate was added to the preparation of belladonna alkaloids, with happy results. The patient became much brighter and more cheerful during the intervals between the attacks. The latter became less frequent (less than one a week), shorter and less severe. They frequently did not progress to the stage of diaphoresis before receding. Ephedrine sulfate had a similar effect.

Examination of the cerebrospinal fluid revealed that it was entirely normal. A roentgenogram of the skull showed nothing significant. An electroencephalogram taken during the interval was essentially similar to that recorded during a "seizure": There was a dominant rhythmic activity of about 8 per second; regulation of frequency was poor at times; occasional 5 per second

waves appeared during apparent sleep; after intravenous injection of sodium amytal there was generalized activity, with a 20 to 25 per second frequency, and the patient went into a deep sleep and did not respond to loud noises; on his awakening waves of low amplitude and random frequency became dominant.

Oral dextrose tolerance tests, made during an interval between attacks and during an attack, gave the following readings:

Time, Hr.	Interval		Attack	
Fasting	Blood, Mg.	Urine	Blood, Mg.	Urine
	89.3	—	111.1	Trace
½	99.0	—	181.8	Trace
1			190.5	Trace
1½	72.7	—		
2			125.0	Trace
2½	82.6	—		
3			121.2	Trace
4			100.0	—

COMMENT

The recent episodic changes which were observed in this case may be considered under two categories: the autonomic and the cataleptic. With the autonomic variations may be included diaphoresis, fever, tachycardia, hypertension and hyperglycemia. While these phenomena suggest a syndrome of sympathetic excitation, it should be noted that the diaphoresis was associated with a warm skin and may represent an attempt at compensation by loss of heat. It is interesting, too, that sodium amytal mitigated the sympathetic manifestations to some extent and, in addition, induced bronchial hypersecretion, an indisputably parasympathetic effect. The preponderance of modern evidence, both experimental and clinical, suggests that autonomic regulation, although influenced by mechanisms existing at all levels, has its seat in the hypothalamus. Two functionally different regions are recognized: an anterior, concerned with the induction of parasympathetic effects, and a posterior, stimulation of which evokes sympathetic phenomena. It is unlikely that the sympathetic release in this case resulted from temporary inhibition of the anterior region, for a parasympathetic response appeared spontaneously and became even more pronounced in the presence of sodium amytal. A more probable explanation of the autonomic outburst is temporary irritation of the posterior region of the hypothalamus. Moreover, the degree of diaphoresis observed in this case was far in excess of what is clinically usual in patients with a temperature of 100 F. and suggests that the irritation proceeded forward to the anterior region and produced a diffuse, mixed autonomic discharge, in which both sympathetic and parasympathetic features appeared.

Akinesia and rigidity together produced in this case fairly typical flexibilitas cerea. The latter, together with mutism, strongly suggested the cataleptic syndrome. The condition resembled catatonia also in that, although mute, the patient was observant and after the passing of the attack could discuss intelligently the events that had occurred in his environment. Postural suggestibility associated with mutism occurs in a number of nosologically different conditions. In hypnosis, hysteria and schizophrenia it is presumed to be psychic in origin—in hypnosis it is considered evidence of successful rapport; in hysteria and schizophrenia, an expression of negativism. The phenomenon has previously been observed in cases of the parkinsonian syndrome (Gerstmann and Schilder[1]), as well as with neoplasms of the diencephalon, and has been produced experimentally in cats by

1. Gerstmann, J., and Schilder, P., cited by Kleitman.[11]

Ingram, Barris and Ranson,[2] who interrupted fiber tracts passing from the pallidum to the hypothalamus in some animals and produced bilateral electrolytic lesions in the posterior hypothalamus in others. Postural suggestibility is usually associated with somnolence in cases of hypnosis, infrequently in cases of schizophrenia and irregularly and unpredictably in cases of organic lesions, either spontaneous or experimental. Sodium amytal is an adjuvant to hypnosis, in which it helps to elicit catalepsy, though it frequently abolishes it in cases of recent schizophrenia. Most patients with long-standing schizophrenic catatonia do not respond to the drug. The effect of amytal is not mentioned in the accounts of cases of organically determined catalepsy, but in my case it had a minimal effect on this state. If one accepts Hoefer's[3] experimental confirmation of Jackson's description of rigidity as "tremor run together" and of tremor as "rigidity spread thin," the fact that in my case attempts to change the position of the limbs encountered cogwheel rigidity and precipitated an increase in the amplitude of the tremor does not absolutely differentiate this form of catalepsy from that occurring with the other, aforementioned conditions. The report of several cases in which full-fledged postencephalitic parkinsonism followed the typical picture of catatonic schizophrenia (Alexander[4]) may or may not represent merely a coincidence. The "still reaction," or immobility response, of animals strongly resembles human catalepsy. Certainly, from the data available one may not conclude that the cataleptic syndrome is the result of a specific physiologic derangement.

The first observation on experimentally induced catalepsy was made by Lewy.[5] In his monkeys, bilateral destruction of the lenticular nucleus was followed by bradykinesia, masking of the facies, sleepiness and loss of initiative. Ingram, Barris and Ranson[2] induced a cataleptic state in cats by producing lesions in the ventral portion of the brain stem in the region extending from the anterior border of the mamillary bodies to the nucleus of the third nerve, with implication of the posterior hypothalamic nucleus. When similar lesions were produced in monkeys,[6] somnolence was a more frequent response than catalepsy. As yet, however, there has been no experimental demonstration of a center irritation or stimulation of which results in catalepsy. The constant sequence of events in the episodes described in the present case, namely, tremor, akinesia, mutism and perspiration, suggests that the temporal interposition of the postural change between the increase in tremulousness and the autonomic phenomena may reflect an anatomic interposition of the locus responsible for the exhibition of catalepsy to the pathway between the structure evoking tremor and that inducing the autonomic manifestations. The observations of Davison[7] indicate that tremor arises as a result of irritation of the zona compacta of the substantia nigra and that rigidity is due to irritation of the zona reticulata of the substantia nigra and of the pallidum, which developmentally

2. Ingram, W. R.; Barris, R. W., and Ranson, S. W.: Catalepsy: An Experimental Study, Arch. Neurol. & Psychiat. **35**:1175 (June) 1936.

3. Hoefer P. F. A.: Physiology of Motor Innervation in the Dyskinesias, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:502, 1942.

4. Alexander, L.: The Fundamental Types of Histopathological Changes Encountered in Cases of Athetosis and Paralysis Agitans, A. Research. Nerv. & Ment. Dis., Proc. (1940) **21**:334, 1942.

5. Lewy, F. H., in Miller, H. R.: Central Autonomic Regulations in Health and Disease, New York, Grune & Stratton, 1942.

6. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch. Neurol. & Psychiat. **41**:1 (Jan.) 1939.

7. Davison, C.: The Role of the Globus Pallidus and Substantia Nigra in the Production of Rigidity and Tremor, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:267, 1942.

is identical with the zona reticulata. Ranson and Ranson [8] described fibers leaving the globus pallidus with the ansa and the fasciculus lenticularis to run into the hypothalamus, where they terminate in the nucleus ventromedialis. The site responsible for the cataleptic phenomena presumably lies along this pathway—between the substantia nigra and the hypothalamus, probably rostral to the pallidum. Although catalepsy appears only inconstantly after section of the pallidohypothalamic tract in association with lesions in the lateral portion of the hypothalamus, this pathway cannot be ruled out as a site responsible for the appearance of catalepsy. Results obtained with experimental extirpation are frequently at variance with clinical observations. For example, although Davison gave a convincing argument based on clinicopathologic observations for the origin of parkinsonian rigidity from lesions of the globus pallidus, Ranson observed no rigidity in monkeys in which he had placed large pallidal lesions. Ranson, however, did attribute masking of the facies and bradykinesia to interruption of pallidohypothalamic fibers. Here, too, confusion arises from the comparison of the results of complete extirpation with those of partial, irritative lesions.

The recurrent, episodic nature of the symptoms in the present case is reminiscent of the case Penfield [9] described in 1929 as one of "diencephalic autonomic epilepsy." The lesion in his case was a tumor in the third ventricle. The seizures were of several minutes' duration and occurred at intervals of several hours, while in my case the "seizures" were of several days' duration and recurred at approximately weekly intervals. Cairns and associates [10] reported a case of akinetic mutism due to an epidermoid cyst of the third ventricle, in which the manifestations were recurrent because the cyst was drained by the surgeon at intervals. Other rhythmic phenomena have been attributed to the diencephalon: as pathologic manifestations, narcolepsy and cataplexy (Kleitman [11]), either of which may be idiopathic or the sequela of epidemic encephalitis; and, as a normal phenomenon, the sleep-waking rhythm, which may be disturbed by an encephalitic lesion. Although lability of the autonomic nervous system and cataleptic phenomena have previously been reported independently in cases of epidemic encephalitis (Wimmer,[12] Neal [13]), I have been unable to find any report in which a fixed seizure pattern implicating both autonomic and postural functions was repeatedly exhibited.

The source of the periodicity in the present case is no less obscure than that in cases of the more usual forms of epilepsy. The medication which was so efficacious in mitigating the symptoms may operate not as an anticonvulsant but as a pharmacologic antagonist, which obscures the seizure pattern and perhaps prevents the development of a vicious cycle. While under medication the patient occasionally became slightly more tremulous and bradykinetic and spoke slowly and softly. As the nurse described it, he seemed to be "trying to have a spell." However, the episode lasted but a few hours, was mild and resolved without the appearance of the autonomic phenomena. No attack was observed to terminate

8. Ranson, S. W., and Ranson, M.: Pallidofugal Fibers in the Monkey, Arch. Neurol. & Psychiat. **42**:1059 (Dec.) 1939.

9. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929; Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941.

10. Cairns, H.; Oldfield, R. C.; Pennybacker, J. B., and Whitteridge, D.: Akinetic Mutism with an Epidermoid Cyst of the Third Ventricle, Brain **64**:273, 1941.

11. Kleitman, N.: Sleep and Wakefulness, Chicago, University of Chicago Press, 1939.

12. Wimmer, A.: Further Studies upon Chronic Epidemic Encephalitis, London, William Heinemann, 1929.

13. Neal, J. B.: Encephalitis: A Clinical Study, New York, Grune & Stratton, 1942.

without medication, and it is possible that sympathomimetic drugs are necessary to interrupt a pathologic cycle. Precipitating agents were not identified. It is unlikely that these phenomena represent exacerbations of virus activity, which is considered by some investigators to be the cause of the frequent intermittent progression of chronic epidemic encephalitis.[14] As previously noted, the cerebrospinal fluid in this case was entirely normal.

SUMMARY

A case of chronic progressive epidemic encephalitis is presented. The feature of interest in this case is a recurrent release of tremor, rigidity and catalepsy, followed by a fixed pattern of autonomic activity. Catalepsy is mentioned as a symptom of both structural and functional disorders of the central nervous system, and the site of its origin is discussed. The condition is related to the diencephalic types of epilepsy of Penfield, as well as to the pathologic rhythmicities of epidemic encephalitis.

Saint Elizabeths Hospital.

14. Stevenson, L. D., in Neal.[18]

Case Reports

ANEURYSM OF THE CIRCLE OF WILLIS, WITH SYMPTOM-FREE INTERVAL OF TWENTY-SEVEN YEARS BETWEEN INITIAL AND FINAL RUPTURE

Report of a Case

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Symonds [1] first stated in 1923 that the exact diagnosis of ruptured aneurysm of the circle of Willis could be made during life and gave significant clinical data to support his statement. Since then this accident has been recognized clinically with a high degree of accuracy. In addition the diagnostic criteria are now so well known that it is often possible to find old cases in which the history revealed signs and symptoms of rupture of aneurysm of the circle of Willis and the patient recovered but the physician failed to make a correct diagnosis. In such cases a diagnosis of "causes unknown" or "spontaneous subarachnoid hemorrhage" has often been made. It seems more correct, in the light of present knowledge, to assume that a leaking aneurysm of the circle of Willis was the etiologic factor. Today it is well accepted that the interval of freedom from symptoms following the first attack of aneurysmal rupture may be days, months or years.[2]

The case reported here is that of a man with an interval of twenty-seven years between the first symptoms of rupture of an aneurysm of the circle of Willis, associated with unconsciousness and xanthocromia of the cerebrospinal fluid, and the final, and fatal, episode. A survey of all the reported cases of this condition (table) reveals that twenty-two years is the longest interval of freedom from symptoms on record, although Souquès (cited by Schmidt [3]) mentioned the case of a patient who had "symptoms of cerebral tumor for 55 years" and who died of a suicidal attempt, with neither examination of the cerebrospinal fluid nor autopsy.

We feel that the case of rupture of an aneurysm of the circle of Willis which is reported here presents the longest symptom-free interval on record between the first, nonfatal, and the final, fatal, attack.

REPORT OF CASE

History.—J. S., a 45 year old white man, married, a Syrian mattress maker, was admitted to the Albany Hospital on Jan. 15, 1939 in a state of unconsciousness. His relatives gave a somewhat vague history of an accident which occurred one week before admission. The patient was said to have received a blow on the head while at work, with resulting transitory unconsciousness. He resumed his work, however, and told no one about this incident until two weeks after his admission to the hospital. Since the accident the patient had suffered from generalized headache, dizziness, nausea and vomiting, which became so severe that he had to leave work two days prior to his admission. On the evening of admission he went into the bathroom and suddenly fell to the floor. The family found him writhing on the floor, unconscious and vomiting intermittently. He was immediately brought to the hospital.

From the Departments of Neurology and Psychiatry and of Pathology of the Albany Hospital and the Albany Medical College.

1. Symonds, C. P.: Clinical Study of Intracranial Aneurysms, Guy's Hosp. Rep. **73**:139-158 (April) 1923.

2. Garvey, P. H.: Aneurysms of the Circle of Willis, Arch. Ophth. **11**:1032-1054 (June) 1934. Bagley, C.: Blood in the Cerebrospinal Fluid: Resultant Functional and Organic Alterations in the Central Nervous System; B. Clinical Data, Arch. Surg. **11**:39-81 (July) 1928.

3. Schmidt, M.: Intracranial Aneurysms, Brain **53**:489-540 (Jan.) 1931.

There was nothing of note in the family history except that his father died at the age of 35, of an unknown cause.

The patient's history was especially significant because of the fact that twenty-seven years previously, on June 12, 1912, he was admitted to the Albany Hospital with the history that six days prior to entry he had suddenly fainted while at work. Thereafter he complained of a constant severe pain just above his eyes and at times inability to see clearly. When he was brought to the hospital he was semistuporous, vomited freely and complained of severe headache. Catheterization was necessary. Unfortunately, no note in regard to the neurologic status could be found in his record. A leukocyte count, on June 19, 1912, revealed a total count of 8,200 per cubic millimeter, with a normal differential count. Urinalysis, on June 13, revealed nothing abnormal. Spinal puncture, on June 19, showed xanthochromic fluid. No report on the pressure, protein content or cell count of the cerebrospinal fluid was given. The patient became conscious on the second day in the hospital, but was restless, complained of severe headache, refused food and for the next three days was much depressed, crying a good deal and saying that he wanted a knife to cut his throat. By the fifth day, however, he felt much better; the headache diminished, and on the eighteenth day after admission it was felt that he could be released. The diagnosis on discharge stated that the cause of illness was unknown.

The interval history was noncontributory. The patient married, had seven children and continued his work as a mattress maker. Apparently, he was in perfect health until the events occurring in the week before his second admission to the hospital, twenty-seven years after the first attack.

Examination.—Physical examination on the second admission revealed that he was well nourished and well developed and of pyknic habitus. He was semistuporous but rather restless. There was a slight, essentially negativistic, response to painful stimuli. The patient was mute. The temperature was 97.4 F.; the pulse rate was 100 and the respiratory rate 15 per minute, and the blood pressure was 132 systolic and 60 diastolic. No bruises, ecchymoses or abrasions were noted. The eyes, ears, nose and throat were normal. The heart and lungs were essentially normal, as were the abdomen, genitalia and extremities.

Neurologic examination showed considerable motor irritability. The patient kept constantly trying to roll over onto his right side, but the movements of the upper and lower extremities on that side were much less pronounced than those on the left. The head tended to turn to the right, with no deviation of the eyes. The right upper extremity was spastic, flexed and semipronated. There was no retraction of the neck, tache cérébrale or other sign of meningeal irritation. The right eyelid was ptosed. The pupils were round and equal and did not react to light. The left optic fundus showed numerous recent hemorrhages, with papilledema. Slight weakness of the right side of the face of central type was noted. Sucking and smacking movements of the lips were present. The tongue appeared normal. The tendon reflexes were active and equal on the two sides. The right cremasteric reflex was absent. There was a positive Babinski sign on the right side, with bilateral ankle clonus. Percussion of the skull gave negative results. No bruit could be heard.

Laboratory Data.—The hemoglobin was 112 per cent (Sahli), the erythrocyte count 5,900,000 per cubic millimeter and the leukocyte count 23,550, with a differential count showing a definite shift to the left. The urine was clear and alkaline, with a specific gravity of 1.016, a 1 plus reaction for sugar and a negative reaction for albumin, bile, acetone and diacetic acid. There were 1 or 2 erythrocytes per low power field. The fasting blood sugar was 165.3 mg., the nonprotein nitrogen 39.4 mg. and the creatinine 1.4 mg. per hundred cubic centimeters. Lumbar puncture, done on the fourth hospital day, yielded xanthochromic, clear fluid, under a pressure of 220 mm. of water. Two cubic centimeters of fluid was slowly removed, the final pressure registering 160 mm. The cell count showed 15 leukocytes and 350 erythrocytes per cubic millimeter. The Pandy reaction was negative. The Kahn reaction was negative. Roentgenograms of the skull on January 16 showed a small area of calcification in the suprasellar region; the posterior clinoid processes were not clearly defined; the sella turcica was normal in size and shape, and the left frontal sinus was not visualized, with diminished transmission of rays through both antrums.

Course of Illness.—A clinical diagnosis of recurrent rupture of an aneurysm of the circle of Willis, probably of the left middle cerebral artery, was made. The patient improved rapidly at first. He regained consciousness on the second day but still vomited a good deal, spoke in an unintelligible mumble and groaned considerably. By the fourth day he was eating and drinking well, speech was not quite clear and he was well oriented but could not remember being brought to the hospital. Neurologic signs had now changed, so that only the slight weakness of the right side of the face and the left fundic hemorrhages remained. However, the patient complained of a general severe headache, with a feeling of tightness localized to

the forehead. The consulting neurosurgeon confirmed the diagnosis of leaking aneurysm of the left middle cerebral artery but felt that surgical intervention was not indicated at this time.

The patient continued to improve but became very restless when told he had to stay in bed. Another leukocyte count, done on January 26, showed 13,800 white cells. It was felt that with further rest in bed there was a fair chance for additional calcification to develop at the site of the rupture, as had apparently happened twenty-seven years before. However, he got out of bed several times on January 28 and 29. On the night of January 29 he began to breathe stertorously and went into a seizure, characterized by champing of the jaws, gritting of the teeth and drooling. The convulsion was followed by vomiting, stupor and restlessness, which required manual restraint. The blood pressure rose to 200 systolic and 100 diastolic. Five minutes later generalized extensor rigidity developed, projectile vomiting appeared and the pupils were constricted and equal but did not react to light. Divergent strabismus was noted, with more pronounced deviation of the right eye laterally. The blood pressure rose to 198 systolic and 94 diastolic; the pulse dropped from 80 to 64 per minute; respirations became irregular, and the patient died two hours after the seizure first appeared.

Necropsy.—The patient appeared somewhat younger than his stated age of 45 years. Nothing unusual was observed on superficial examination. The pupils were regular and of the same shape and size, measuring 0.7 cm. in diameter. Autopsy was limited to examination of the cranial cavity.

Brain: The dura mater and the leptomeninges over the vertex of the brain were not abnormal. At the base of the left frontal lobe, however, there were a focus of organized blood clot, in the subdural space, and old pachymeningitis haemorrhagica interna. This focus of organized hemorrhage surrounded a hard, almost bony, mass, about 0.8 by 0.8 by 0.3 cm., located in the meninges and the superficial cortex of the left frontal lobe, about 1 cm. lateral to the crista galli. The mass was adherent to the surface of the left frontal lobe, and it was difficult to separate the dura from it. No fresh blood was observed in the subarachnoid space in this area. The focus of calcification and old organized hemorrhage was somewhat anterior to the aneurysm, which will be described later.

When the brain was lifted carefully from the cranial cavity, a recent massive hemorrhage into the subarachnoid space was revealed, with collections of clotted blood in the cisterna magna and in the basal cisterns about the cerebral peduncles and pons. The brain was then removed from the cranial cavity and carefully examined. In the search for the source of the recent hemorrhage, the arteries of the circle of Willis were dissected out. At the junction of the internal carotid artery with the anterior and middle cerebral arteries and the posterior communicating branch on the left side, a small saccular aneurysm was noted. It measured 1 by 0.6 by 0.6 cm. and was firmly embedded in the underlying cerebral cortex. The arteries in general showed only a few small and superficial, yellowish atherosclerotic patches, without any evidence of calcification. Their lumens were not narrowed. There was no evidence of vascular syphilis.

The left frontal lobe seemed to be a mere shell filled with clotted blood. When the base of the brain was examined more closely, the aforedescribed bony mass in the inferior cortex of the left frontal lobe stood out clearly. The mass suggested an old calcified hemorrhage.

The brain was examined further after fixation in a 10 per cent concentration of solution of formaldehyde U. S. P. The aneurysm was exposed by dissecting away a small portion of the wall at the tip of the left temporal horn. It was then seen to project into the brain in the region of the left anterior perforated substance. Dissection also demonstrated that the recent hemorrhage must have occurred from the tip of the aneurysm, since it was here that most of the fresh blood was seen. The surrounding brain substance was necrotic.

The lateral wall of the left anterior horn was dissected away, and a large focus of hemorrhage was seen in the region of the left basal ganglia. It extended forward to involve part of the frontal lobe. In all, the hemorrhage occupied an area about 6 by 4 by 3 cm. The entire ventricular system was filled with recently clotted blood.

Microscopic Examination.—Sections from various parts of the brain confirmed the impression obtained at autopsy, namely, that of a recent hemorrhage, explosive in character, involving the subarachnoid space, the adjacent cerebral tissues and the ventricular system. The hemorrhage resulted from the rupture of an aneurysm at the junction of the anterior and the middle cerebral artery on the left side. In addition to the hemorrhage, there was the focus of old pachymeningitis haemorrhagica interna at the base of the left frontal lobe, which was confirmed by histologic examination. The calcified mass seen in the roentgenogram, and noted also at autopsy, was observed to be a focus of ossification with well constructed bony spicules, which still showed fibroblastic and osteoblastic activity. In this focus there was a large amount of granular brownish pigment, much of which was hemosiderin. Sections through several of the arteries of the circle of Willis outside the aneurysm showed evidence of slight arteriosclerosis. There was no histologic evidence of syphilis.

Data on Significant Reports in the Literature of Cases of Aneurysm of the Circle of Willis

	Age, Yr.	Sex	Evidence of Initial Hemorrhage or Leak	Initial Spinal Puncture	Duration of Free Interval, Yr.	Final Status	Postmortem Observations	Author
1	50	F	Sudden ocular palsy; involvement of fifth nerve	Not stated	6	Still living*	.....	Nattrass: Lancet **2**:915 (Oct 21) 1933
2	53	F	Decreased vision in right eye; violent pains on right side of head	Not Stated	16	Dead	.....	Schmidt [3]
3	65	?	"Symptoms of cerebral tumor for 55 years"	Not stated	55 (?)	Suicide	.....	Souquès [8]
4	41	F	"Headaches"	Not stated	2	Dead	Aneurysm of left middle cerebral artery	Harper: Brit. M. J. **1**:13 (Jan. 2) 1932
5	29	M	Headache; vomiting; unilateral ptosis	None	9	Still living*	.....	Bramwell: Edinburgh M. J. **103**: 689 (Dec.) 1931
6	12	M	Headache; ptosis of left eyelid; diplopia	None	5	Still living*	.....	Bramwell
7	42	F	Transient hemiplegia	None	17	Dead	Ruptured aneurysm of left posterior cerebellar branch of basilar artery	Fearnsides: Brain **39**:224 (Oct.) 1916
8	41	F	"Headaches"; blindness 3 yr.	Not stated	16	Dead	Ruptured aneurysm of right anterior cerebral artery	Fearnsides
9	67	F	Right hemiplegia; motor aphasia	Not stated	21	Dead	Ruptured aneurysm of left middle cerebral artery	Fearnsides
10	42	?	.....	Not stated	23	Dead	Calcification at area of the original rupture	Bagley: Arch Surg. **11**:39 (July) 1928
11	34	?	.....	?	5	Still living*	.....	Bagley
12	49	M	Headache; vomiting; coma..	Not stated	17	Dead	Aneurysm of left anterior cerebral artery	Merritt and Staricoff: M. J. Australia **2**:387 (Sept. 22) 1934
13	48	F	"Symptoms of brain tumor"	None	7	Patient living 6 yr. after removal of aneurysm of internal carotid artery		Gardner: S. Clin. North America **16**:1019 (Aug.) 1936
14	36	?	?	?	7	Dead	Aneurysm of left posterior communicating artery	Strauss and others: Arch. Neurol. & Psychiat. **27**:1080 (May) 1932
15	24	M	Hemiplegia	?	7	Dead	Aneurysm of basilar artery	McDonald and Korb: Arch. Neurol. & Psychiat. **42**:298 (Aug.) 1939
16	40	F	Subarachnoid hemorrhage; headache; onset with general convulsions; transient hemiplegia	†	2	Still living*	.....	Garvey [2]

* Status at time of publication.

† 300,000 red cells, 480 white cells, 85% hemoglobin, Pandy positive, Wassermann negative.

Diagnosis.—These observations lead to the anatomic diagnosis of a congenital aneurysm of the circle of Willis at the junction of the anterior and the middle cerebral artery, on the left side, with evidence of old and recent rupture. Evidence of the old rupture was seen in the healed area of pachymeningitis haemorrhagica interna and the focus of ossification slightly anterior to the aneurysm. This rupture was undoubtedly the cause of the episode twenty-seven years before. The recent rupture resulted in massive hemorrhage into the subarachnoid space, the cerebrum and the ventricular system and was the cause of the patient's death.

COMMENT

This case is presented for two reasons. First, as is apparent from the accompanying table, it represents the longest recorded period of survival from a ruptured aneurysm of an artery of the circle of Willis. Second, it serves to reemphasize the ability of the organism to make use of repair processes in the prevention of an otherwise fatal rupture of congenitally weak blood vessel walls. The organizing hemorrhage of the dura mater (pachymeningitis haemorrhagica interna) in the region of the aneurysmal rupture which occurred twenty-seven years ago, as well as the ossification of the old blood clot, undoubtedly served as a protective mechanism against future accidents from the damaged vessel. It is improbable that the patient could have led a fairly normal and active life for twenty-seven years without intercurrent symptoms, not to mention another cerebral "accident," had not this superimposed repair process developed.

Another point of interest is the problem of neurosurgical intervention in a case of this type, when it is first encountered in the emergency room. Although the neurosurgeon's efforts to combat this condition are to be commended, it must be conceded that a spontaneous "cure" of twenty-seven years merits considerable respect for Nature's successful therapy.

SUMMARY

A case of aneurysm of an artery of the circle of Willis with a free interval of twenty-seven years and final rupture, with fatal hemorrhage, is presented and the literature on the subject tabulated.

Albany Hospital.

News and Comment

AMERICAN SOCIETY FOR RESEARCH IN PSYCHOSOMATIC PROBLEMS

The first annual meeting of the American Society for Research in Psychosomatic Problems was held in Detroit at the Hotel Statler, May 9 to 11, 1943, with the American Psychiatric Association. The program included a closed military session on "The Unfit; Not to Exclude and How to Use Them," of which Col. Roy D. Halloran, Chief of the Neuropsychiatric Division of the Surgeon General's Office, was chairman. Papers were presented by Col. Leonard Rowntree, Dr. M. R. Harrower-Erickson and Major Henry W. Brosin. The reading of these papers was followed by a panel discussion, in which many prominent members of the armed forces participated.

An open meeting on the subject of gastrointestinal dysfunction was also held, and Dr. Walter L. Palmer, professor of medicine at University of Illinois College of Medicine, presided. A report of these meetings will be published in an early issue of *Psychosomatic Medicine*.

In addition, a meeting was held with the American Psychiatric Association on May 15, 1943, in Detroit. The papers read at this meeting dealt for the most part with new methods of psychosomatic diagnosis, including new Rorschach technics and a new electronic method for measuring and recording deviations in psychosomatic functions.

At the business meeting, the following officers were elected: Adolf Meyer, M.D., honorary president; Tracy Putnam, M.D., president; Winfred Overholser, M.D., president-elect; Edwin G. Zabriskie, M.D., secretary-treasurer, and Ruth Potter, assistant secretary-treasurer. Councillors elected were: Dana Atchley, M.D.; Arlie Bock, M.D.; Flanders Dunbar, M.D.; Jules Masserman, M.D.; William Ogburn, Ph.D.; Kurt Richter, M.D.; Milton Senn, M.D.; Harry Solomon, M.D., and Edward Weiss, M.D.

A constitution was unanimously adopted, and the following committees on research were appointed: (1) committee on psychosomatic problems in obstetrics and gynecology; (2) committee on psychosomatic problems in early infancy and childhood; (3) committee on psychosomatic problems in physiologic mechanisms; (4) committee on psychosomatic implications of animal experimentation; (5) committee on psychosomatic teaching in medical schools; (6) committee on psychoanalytic research in psychosomatic problems; (7) committee on psychosomatic approach to social and cultural problems; (8) committee on psychosomatic problems in war medicine; (9) committee on psychosomatic problems in internal medicine, and (10) committee on psychosomatic problems in industrial medicine.

The functions of these committees are as follows: to correlate and initiate psychosomatic research in their respective fields; to present an annual report, and to suggest programs for meetings in conjunction with sessions of other medical societies.

Great interest and enthusiasm were expressed by many persons in the society, particularly by members of the armed forces because of the widespread incidence of psychosomatic dysfunction which exists in the present military emergency and the present lack of research and therapeutic facilities. It is expected that the committee on war medicine, particularly, will offer suggestions toward the solution of this situation.

CENTRAL NEUROPSYCHIATRIC ASSOCIATION

The executive committee of the Central Neuropsychiatric Association voted last fall to cancel all meetings for the duration of the war, so that a meeting is not planned for 1943.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

DISTRIBUTION OF THE TASTE BUDS ON THE TONGUE OF THE KITTEN. E. RUSSELL HAYES and RUSH ELLIOTT, J. Comp. Neurol. **76**:227 (April) 1942.

The lingual nerve of one side was cut in 3 young kittens, and a section 5 to 7 mm. long was removed. Sixteen to nineteen days later the animals were killed; the epithelium of the dorsum of the tongue was prepared for cell study, and the taste buds were counted. The area innervated by the chorda tympani fibers of the facial nerve in the kitten is similar to that in man, namely, the anterior two thirds of the tongue. The gustatory fibers associated with the lingual nerve on one side pass beyond the midline of the tongue, so that taste buds near the midline have a bilateral innervation. There is a slight overlap of the glossopharyngeal nerve with the facial nerve in the area immediately craniad to the circumvallate papillae. The average number of taste buds innervated by the lingual nerve was estimated to be 1,150 for the entire tongue.

FRASER, Philadelphia.

THE DORSAL LONGITUDINAL FASCICULUS IN DIDELPHIS VIRGINIANA. ELIZABETH L. THOMPSON, J. Comp. Neurol. **76**:239 (April) 1942.

Ten series of sections of the brain of the opossum were available for this study. The dorsal longitudinal fasciculus lies wholly within the ventral and ventrolateral portions of the central gray substance. It consists mainly of descending tracts. Its fibers are for the most part nonmyelinated or lightly myelinated. The tract originates from a number of different sources in the diencephalon and passes caudal for an undetermined distance into the spinal cord. Its rostral connections suggest to Thompson that the dorsal longitudinal fasciculus coordinates the activities of nuclei of the cranial nerve.

FRASER, Philadelphia.

THE PRETECTAL REGION OF THE RABBIT'S BRAIN. HARTWIG KUHLENBECK and RUTH N. MILLER, J. Comp. Neurol. **76**:323 (April) 1942.

This study is based on myelin and Nissl preparations of the pretectal region of the rabbit brain. Graphic reconstructions were made of the more important pretectal nuclei. The nuclei of the pretectal region were classified into four groups: (1) diencephalic pretectal cell masses; (2) mesencephalic derivatives of tectal origin; (3) thalamic cell masses, and (4) a group of tegmental derivatives. The fiber connections of the pretectal region were grouped into six main systems: (1) the arciform system, connecting the pretectal nuclei with the cortex, the thalamus, the epithalamus, the lateral part of the hypothalamus, the geniculate bodies, the tectum and the tegmentum; (2) the longitudinal system, which reaches from the mesencephalon to the caudal portion of the diencephalon; (3) the caudal dorsoventral, or perpendicular, system, which passes through the pretectal cell masses and forms a connection between the tectum and the tegmentum; (4) the caudal transverse system, between the medial and the lateral pretectal cell masses and other centers; (5) the periventricular system, and (6) the commissural fibers of the posterior, habenular, supraoptic and supramamillary commissures.

ADDISON, Philadelphia.

VASCULAR SUPPLY OF THE MONKEY'S SPINAL CORD. A. L. SAHS, J. Comp. Neurol. **76**: 403 (June) 1942.

Injections of india ink into the spinal cords of Macaca mulatta were studied grossly in sagittal and in cross sections. Each of the two vertebral arteries gives off four to six twigs, which enter into the formation of the anterior spinal artery and the posterior spinal arteries. The segmental radicular arteries contribute most of the blood supply to the spinal cord. Approximately ten significant segmental arterial branches reach the cord by way of the anterior roots and six by way of the posterior roots. Eight to ten veins course through the anterior roots and twelve to fourteen through the posterior roots.

ADDISON, Philadelphia.

THE CHROMATIN CONTENT OF NERVE CELLS IN MAN AND IN THE MOUSE WITH SPECIAL REGARD TO THE RÔLE OF THE NUCLEOLUS. WARREN ANDREW and NANCY VALÉRIE ANDREW, J. Comp. Neurol. **76**:423 (June) 1942.

The cerebral cortex and the cerebellum of 6 white mice 65 days of age, and litter mates, were studied by means of Feulgen's nuclear reaction. One animal was used as a control, and the other 5 were partially starved for twenty-eight days. The cerebral cortex and the cerebellum of 2 human beings who died in a state of inanition were similarly studied. The normal appearance of the nucleus of the nerve cells showed that the greater part of its chromatin was arranged as several conspicuous, variously shaped particles on the periphery of the nucleolus, while the rest of the nucleus was almost devoid of chromatin. In malnourished animals the chromatin on the nucleolus was reduced to a thin film, and the chromatin in the body of the nucleus was greatly increased. A similar distribution of chromatin was observed in Purkinje cells of the "pyknotic" type even in normal animals. No visible morphologic connection between the chromatin of the nucleolus or nucleus and the Nissl substance was observed.

ADDISON, Philadelphia.

MELANIN PIGMENT IN THE BRAIN OF THE GORILLA. ALEXANDER ADLER, J. Comp. Neurol. **76**:501 (June) 1942.

Adler examined the brain of an adult gorilla microscopically and compared the sections of the substantia nigra with those of a chimpanzee and of man. Pigment in the substantia nigra is dark brown and, although all the cells contain pigment, variable in amount. The pigment is darker and more intense and the granules are larger in the gorilla than in the chimpanzee. The pigment is lighter and less intense and the granules are smaller in the gorilla than in adult man. The locus caeruleus is light brown, and the granules are dust-like and much finer than in the substantia nigra. All the cells of the locus caeruleus contain melanin pigment, but the granules are widely dispersed and sparse. There are only a few scattered melanin granules in the melanophores of the pia of the gorilla. Adler compares the amount of pigment in the ganglion cells of the substantia nigra and the locus caeruleus with that present in corresponding structures of the brain of a 4 year old child. However, the melanin of the substantia nigra of man in postencephalitic parkinsonism, a disease associated with loss of pigmentation of the substantia nigra, is different in color and distribution from that observed in the animals examined.

ADDISON, Philadelphia.

CORTICAL LAMINATION IN A POLYPROTODONT MARSUPIAL, PARAMELES NASUTA. A. A. ABBIE, J. Comp. Neurol. **76**:509 (June) 1942.

Abbie studied the entire cerebral cortex of the common long-nosed bandicoot. Graphic reconstruction of the medial, dorsal, lateral and ventral aspects of the right hemisphere were made. Distribution of the cortical areas was plotted from both coronal and sagittal sections. Fifteen formations were delimited. Six formations were related to the hippocampus and eight to the piriform cortex; the other was the anterior olfactory nucleus, which appeared to be related to both. The claustrum was seen to merge dorsally with laminas V and VI of the parapiriform cortex. Ventrally and posteriorly the cells of the claustrum were traceable as a tenuous string down and back to the amygdaloid fissure. The cortical contribution to the amygdaloid nucleus seemed to come mainly, or entirely, from the posterior piriform cortex.

FRASER, Philadelphia.

THE ONTOGENETIC DEVELOPMENT OF THE RABBIT'S DIENCEPHALON. JERZY E. ROSE, J. Comp. Neurol. **77**:61 (Aug.) 1942.

Rose studied the diencephalon of rabbit embryos from 4 to 65 mm. in length, as well as that of older embryos and newborn and adult animals. For the younger stages cardboard reconstructions of the forebrain were prepared. Rose describes the ontogeny of the diencephalon by the use of M. Rose's nomenclature. Three areas were distinguished in the thalamic plate of the diencephalon—a dorsal, a middle and a ventral region. The habenular, prebigeminal and paraventricular nuclear groups developed from the dorsal region. This region Rose calls the independent thalamus, because its nuclei remain unchanged after ablation of the telencephalon. The middle region develops later in life, in harmony with the later development and differentiation of the telencephalon. The independent thalamus does not keep pace with the forward growth of the middle region and thus appears to be displaced backward. The ventral thalamus, or the connecting thalamic area, gives rise to the reticular complex, the ventrolateral geniculate nucleus and the suprahypothalamic group. The hypothalamic plate could be identified in the 16 mm. embryo. Three divisions are distinguishel: (1) the anterolateral

hypothalamic area, from which develop the globus pallidus, the diagonal area and the lateral hypothalamic group; (2) the central hypothalamic area, from which most of the hypothalamic nuclei develop, and (3) the dorsal hypothalamic area, or subthalamus, from which the suprapeduncular complex and the corpus subthalamicum develop.

ADDISON, Philadelphia.

THE ORIGIN OF FIBERS TO THE GRAPE-LIKE ENDINGS IN THE INSERTION THIRD OF THE EXTRA-OCULAR MUSCLES. KENDALL B. CORBIN and R. K. OLIVER, J. Comp. Neurol. **77**:171 (Aug.) 1942.

Corbin and Oliver used 30 adult cats in this study. The superior cervical sympathetic ganglia were removed bilaterally in 6 cats and unilaterally in 3 cats. One to twelve lesions were placed in the brain stem by means of the Horsley-Clarke stereotaxic instrument; these were so distributed as to destroy in 10 cats the mesencephalic root and nucleus of the trigeminal nerve from the level of the trochlear nucleus to just rostral to the posterior commissure. In 5 cats the central gray substance was destroyed, and in 15 cats various parts of the oculomotor nucleus were destroyed. Three to twenty-one days later, the third, fourth and sixth cranial nerves and the massenteric branch of the fifth nerve were removed and treated with osmium tetroxide. The muscles were stained with methylene blue (methylthionine chloride) or by the pyridine-silver method. Complete bilateral destruction of the mesencephalic root of the fifth nerve rostral to the nucleus of the fourth nerve did not result in degeneration of myelinated fibers in the third, fourth or sixth cranial nerves or in the destruction of the grapelike endings present in the insertion third of the extrinsic ocular muscles. Lesions which destroyed the large cell portion of the oculomotor nucleus or the trochlear nucleus caused degeneration of the grapelike endings, as well as of the motor end plates. These observations suggest that the cells of origin for the supposedly afferent fibers to the extrinsic ocular muscles were located close to or within areas occupied by the motor cells of the oculomotor nerves.

ADDISON, Philadelphia.

FURTHER ATTEMPTS TO TRACE THE ORIGIN OF AFFERENT NERVES TO THE EXTRINSIC EYE MUSCLES. KENDALL B. CORBIN and FRANK HARRISON, J. Comp. Neurol. **77**:187 (Aug.) 1942.

Corbin and Harrison explored the brain stem in 5 adult cats with a recording electrode in the Horsley-Clarke stereotaxic instrument, while the branch of the oculomotor nerve going to the inferior oblique muscle was stimulated with single shocks of low intensity. Action potentials were recorded by oscillograph, and the brain stems were subsequently studied microscopically. Response was obtained only when the recording electrode was in or close to the oculomotor nucleus. From no other parts of the mesencephalon was it possible to record action potentials during such stimulation. The experiments support the conclusion that the cells of origin of the fibers terminating as the grapelike endings in the insertion third of the extraocular muscles of the cat are located within the brain stem close to, or within, the area occupied by the oculomotor neurons.

ADDISON, Philadelphia.

IMMEDIATE EFFECTS OF 31 R OF X-RAYS ON THE DIFFERENT STAGES OF MITOSIS IN NEUROBLASTS OF CHORTOPHAGA. J. GORDON CARLSON, J. Morphol. **71**:449 (Nov.) 1942.

A latent period lasting thirty to sixty minutes follows treatment of neuroblasts of the grasshopper (Chortophaga viridifasciata, De Geer) with 31 r of roentgen radiation. During this period the normal course of mitosis is not altered. Cells in advanced middle prophase and initial late prophase show the greatest sensitivity. Neuroblasts are stopped in these stages for about one hundred and eighty minutes, after which recovery sets in. Cells treated in early prophase are not prevented from advancing into middle prophase, but their mitotic progress is slowed and is finally stopped as they reach advanced middle prophase. This gradually increasing effect, terminating in eventual cessation, is evidence of a latent effect of roentgen irradiation. Mitosis in cells in metaphase, anaphase and early telophase is not affected by this dose of roentgen rays. Carlson suggests that roentgen radiation may alter the mitotic progress of cells mainly through effects on the prophase chromosomes.

REID, Boston.

Physiology and Biochemistry

THE NATURE OF THE GLYCEROPHOSPHORIC ACID PRESENT IN PHOSPHATIDES. J. FOLCH, J. Biol. Chem. **146**:31, 1942.

The methods of isolation hitherto used to prepare glycerophosphoric acid from phosphatides hydrolyzed with alkali or acid yield optically inactive mixtures of alpha and beta

glycerophosphoric acids, in proportions which depend on the conditions of hydrolysis. Hence available data do not provide evidence as to whether the glycerophosphoric acid in phosphatides is the alpha or the beta form.

PAGE, Indianapolis.

BRAIN CEPHALIN, A MIXTURE OF PHOSPHATIDES. J. FOLCH, J. Biol. Chem. **146**:35, 1942.

The phosphatide fraction of brain called cephalin was formerly believed by some investigators to be a definite compound of glycerophosphoric acid with two molecules of fatty acids and one molecule of ethanolamine. Folch now adds that the individual phosphatides in such a fraction exhibit differences in their respective solubilities in mixtures of chloroform and alcohol. This fact is made use of for the separation from cephalin of three different fractions, namely, (*a*) phosphatidyl serine, (*b*) a compound which has the composition formerly attributed to the whole cephalin, and which is called phosphatidyl ethanolamine, and (*c*) a mixture of phosphatides, one or more of which contain inositol as a constituent. The fraction containing inositol phosphatide is less soluble in alcohol than either phosphatidyl serine or phosphatidyl ethanolamine; from it have been isolated, besides inositol, glycerophosphoric acid and serine, the presence of which indicates the probable presence of phosphatidyl serine in the mixture. Phosphatidyl ethanolamine, unlike the cephalin to which its composition was formerly assigned, is freely soluble in alcohol. From it have been isolated ethanolamine and glycerophosphoric acid. With the exception of phosphatidyl ethanolamine, the phosphatides in the cephalin fraction of brain lipids are strongly acidic and are isolated from brain as salts of potassium and sodium when treatment with mineral acid is avoided in the isolation. Treatment with hydrochloric acid removes the alkali cations. The method described for separating the phosphatides of cephalin is effective only when applied to material that has not had its mineral bases removed.

PAGE, Indianapolis.

THE EFFECT OF HEXOSES AND PENTOSES ON THE FORMATION IN VITRO OF PHOSPHOLIPID BY BRAIN TISSUE AS MEASURED WITH RADIOACTIVE PHOSPHORUS. H. SCHACHNER, B. A. FRIES and I. L. CHAIKOFF, J. Biol. Chem. **146**:95, 1942.

With the aid of radioactive phosphorus, it has been demonstrated that surviving slices of liver, kidney, brain and brain homogenates are capable of synthesizing phosphatides from inorganic phosphate. This conversion in vitro (inorganic P^{32} to phosphatide P^{32}) by surviving brain slices is greatly increased by the addition of the hexoses dextrose, galactose, mannose and fructose. This increase in recovery of radiophosphatide is interpreted as being due to an increased rate of formation of phosphatide or of a phosphorus-containing phosphatide precursor. The addition of pentoses failed to increase the recovery of radiophosphatide. The stimulating effect of the hexoses on the recovery of radiophosphatide is abolished when tissue organization is disrupted by homogenization. The stimulating effect of the hexoses on the recovery of radiophosphatide does not occur under anaerobic conditions.

PAGE, Indianapolis.

STUDIES ON THE METABOLISM OF BRAIN SUSPENSIONS: II. CARBOHYDRATE UTILIZATION. K. A. C. ELLIOTT, D. B. M. SCOTT and B. LIBET, J. Biol. Chem. **146**:251, 1942.

Elliott, Scott and Libet report on a study of the extent to which the respiration of isotonic suspensions of brain tissue can take place at the expense of dextrose, lactate or pyruvate. They show that brain tissue can metabolize noncarbohydrate materials, particularly when the normal substrate is lacking. Consumption of noncarbohydrate substances by the brain may be an important aspect of the insulin shock treatment for psychoses. Differences in behavior between dextrose and lactate as substrates for respiration of brain tissue have been noted. These differences may help to explain the observations by other workers that lactate is readily utilized by brain tissue in vitro and yet does not seem to support normal functions of the brain in vivo. Adaptations of known methods for the determination of dextrose, total carbohydrate and lactic, pyruvic and acetic acids in isotonic suspensions of rat brain have been worked out. Corrections are shown to be necessary in most cases when pyruvate is present. In the absence of added substrate, oxidation of noncarbohydrate materials accounts for most of the respiration of isotonic brain suspensions. In the presence of dextrose, the oxidation of noncarbohydrate materials by a brain suspension is largely suppressed, and nearly all the respiration takes place at the expense of dextrose. The maximum rate of respiration occurs in the presence of 10 mg. of dextrose per hundred cubic centimeters of the suspension. In the presence of pyruvate, the respiration can be accounted for completely by utilization of pyruvate. About 14 per cent of the pyruvate utilized is converted to acetate, and an approximately equivalent amount of lactate is formed. Respiratory rates

equal to those with dextrose are obtained in the presence of 10 mg. per hundred cubic centimeters of pyruvic acid. When pyruvate and dextrose are both present, more pyruvate than dextrose disappears. With suspensions from normal brains, added lactate is not as efficient as dextrose or pyruvate in displacing noncarbohydrate oxidations, but with brains from insulinized animals, oxidation of added lactate can account for approximately the entire respiration. Higher concentrations of lactate than of dextrose or pyruvate are required to produce the maximum respiratory rate. When lactate and dextrose are both present, dextrose only is utilized, while the concentration of lactate is usually not decreased. No appreciable utilization of carbohydrate other than dextrose could be detected in the presence or absence of the added substrates, and there was no significant sign of synthesis of carbohydrate from lactate or pyruvate. Acetic acid has no effect on the oxygen uptake or the respiratory quotient and is not utilized by brain suspensions.

PAGE, Indianapolis.

THE INFLUENCE OF PARENTERAL ADMINISTRATION OF α-TOCOPHEROL PHOSPHATE ON THE METABOLIC PROCESSES IN DYSTROPHIC MUSCLE. O. B. HOUCHIN and H. A. MATTILL, J. Biol. Chem. **146**:309, 1942.

Biopsy experiments on rabbits have shown that parenteral administration of alpha tocopherol phosphate caused the high oxygen consumption of dystrophic rabbit muscle to drop 34 per cent within the first hour; the fall continued during four hours to 49 per cent, a decrease to nearly normal figures. A sharp decline in the creatine content of muscle accompanied the lowering of oxygen consumption during the first two hours; at the end of four hours there was a slight rise, but the figures were still far below the initial, already low, level of dystrophic muscle. This result is the opposite of the final effect of tocopherol on the creatine content of dystrophic rabbit muscle after cure. The chloride concentration of the muscle remained high throughout and was not immediately influenced by tocopherol. The biopsy operation itself had no effect on either the oxygen uptake or the creatine content of normal muscle. Alpha tocopherol phosphate had little, if any, effect on normal muscle; the only action was a slight increase in oxygen consumption after four and six hours. The data are interpreted to mean that alpha tocopherol phosphate is intimately connected with the complicated, and yet unknown, enzyme systems by which the physiologic integrity of muscle tissue is maintained.

PAGE, Indianapolis.

THE IN VITRO EFFECT OF α-TOCOPHEROL AND ITS PHOSPHATE DERIVATIVE ON OXIDATION IN MUSCLE TISSUE. O. B. HOUCHIN, J. Biol. Chem. **146**:313, 1942.

The high oxygen consumption of dystrophic rabbit and hamster muscle slices was lowered 40 per cent, and toward normal, by the addition of alpha tocopherol phosphate to the medium. There was no influence on normal muscle slices. The Q_{O_2} of muscle slices after immersion for three minutes in boiling water was negligible and was not altered by the addition of alpha tocopherol phosphate. Results with alpha tocopherol in vitro were inconclusive. Mincing and homogenizing lowered the Q_{O_2} of both normal and dystrophic muscle. Although the Q_{O_2} of the dystrophic muscle slices was 60 per cent higher than the normal, the minced and homogenate gave figures for the Q_{O_2} which were, respectively, identical for normal and dystrophic muscle. The succinoxidase activity of dystrophic hamster muscle was 160 per cent above that of normal muscle and was somewhat proportional to the degree of dystrophy. The difference between normal and paralyzed suckling rat muscle was much less. The high activity was malonate sensitive. Alpha tocopherol phosphate reduced the succinoxidase activity of dystrophic muscle by 59 per cent, and toward normal; this agreed with the decrease in Q_{O_2} of muscle slices produced by addition of alpha tocopherol phosphate in vitro and in vivo. Alpha tocopherol, either alone or with desoxycholic acid, failed to influence the oxygen uptake, owing to succinoxidase activity. The possible role of alpha tocopherol phosphate in the metabolism of skeletal muscle is briefly discussed.

PAGE, Indianapolis.

BEHAVIOURAL DISTURBANCES OF VOMITING AND MICTURITION IN CONDITIONED CATS. S. DWORKIN, J. O. BAXT and E. DWORKIN, Psychosom. Med. **4**:75 (Jan.) 1942.

Dworkin, Baxt and Dworkin believe that weak stimuli, such as attenuated tones, particularly those of near-threshold intensity, are ideally designed to cause conflict between the fundamental nervous functions of excitation and inhibition. Listening to such tones involves the finest possible discrimination between the presence and the absence of sound. The procedure of exposing cats to pure tones of threshold loudness was found to precipitate a complex and enduring disturbance in behavior. In 1 cat this culminated in episodes of vomiting, while in 2 others uncontrolled micturition occurred in the conditioning cage. Overt behavioral dis-

turbances did not occur early in the exposure to the conflict situation but appeared only after many repeated trials over a period of months. The authors emphasize the fact that the animals in these experiments were subject to testing for a period of about forty-five minutes daily, with only three threshold stimuli presented during that period. Therefore, the breakdown was evidently the result of some cumulative damage in the nervous system. The authors feel certain that their results are explainable on the basis of irradiation of inhibition and remote positive induction. The behavioral disturbances in cats may vary greatly, the differences depending on such factors as the precipitating cause and the animal's previous history, as well as on species or individual constitution. They find that neither the vomiting nor the excessive general bodily activity is influenced by bromide sedation. On the other hand, prolonged rest from training or training with loud tone stimuli has a decided beneficial effect.

SCHLEZINGER, Philadelphia.

TRANSMISSION OF IMPULSES IN THE MOTOR END PLATE OF WARM-BLOODED ANIMALS. H. SCHAEFER and H. GÖPFERT, Arch. f. d. ges. Physiol. **244**:459, 1941.

Action currents, transmission of impulses and inhibition were studied on the motor end plates of cats and guinea pigs by means of a cathode ray oscillograph. An "end plate current" was demonstrated in pure form by inhibiting the activity of the muscles by high frequency stimuli. On continuous stimulation this end plate current drops to a constant level, which remains unchanged after stimulation for one-half hour. It is unassociated with changes in the mechanical state of the muscle. This current of the motor end plate does not show fatigue, is not paralyzed by curare but is sensitive to asphyxia. Supermaximal stimulation close to the muscle or administration of prostigmine may induce "spontaneous" rhythmic discharges of the motor end plate. Two types of such discharges were observed: those which follow stimulation immediately and those which occur several seconds later. The end plate may be regarded as a model of convulsive discharges. The maximal frequency of the nerves of warm-blooded animals lies not much above 100 Hertz per second, and that of the muscle on indirect stimulation, at 35 to 60 Hertz per second. The efficiency of the muscle at high frequencies is better on direct than on indirect stimulation. The muscle of warm-blooded animals is not superior to that of cold-blooded animals on stimulation with high frequencies.

SPIEGEL, Philadelphia.

Psychiatry and Psychopathology

MENTAL SYMPTOMS IN NARCOLEPSY. MAX LEVIN, Am. J. Psychiat. **98**:673 (March) 1942.

Levin states that the key to the pathogenesis of narcolepsy lies in the experiments of Pavlov on cerebral inhibition and sleep. Both Pavlov's animals and narcoleptic patients fell asleep under the influence of inhibitory stimuli.

Levin believes that the thinking difficulties common in narcolepsy are due to excessive inhibition. He reports a case of difficulty in learning and 2 cases of memory defects associated with narcolepsy and ascribes the disturbances to the inhibition of a conditioned reflex.

FORSTER, Boston.

THE PROBLEM OF BRAIN TUMOR IN PSYCHIATRIC DIAGNOSIS. HOWARD D. MCINTYRE and AURELIA P. MCINTYRE, Am. J. Psychiat. **98**:720 (March) 1942.

For the failure to recognize tumors of the brain in psychiatric patients, McIntyre and McIntyre stress the following causes: lack of consciousness of brain tumor; neglect to obtain a detailed neurologic history and examination; failure to realize that headache, vomiting and choked disk are not early signs of tumor; too much reliance on the absence of increased intracranial pressure, as measured by the manometer, on the finding of a normal protein content of the spinal fluid and on normal roentgenograms of the skull, and failure to make air injection studies. The authors utilize cases to illustrate the various problems arising in the evaluation of the presence of brain tumors in psychiatric conditions. That a brain tumor may occur in a patient with a psychosis is illustrated by the case of a schizophrenic patient in whom a pituitary tumor developed. In the authors' cases, the following tumors of the brain were incorrectly diagnosed as psychiatric disorders, the erroneous psychiatric diagnosis being given in parentheses: (1) meningioma of the anterior cerebral fossa (Alzheimer's disease); (2) meningioma of both frontal lobes (arteriosclerotic dementia); (3) meningioma of the left occipital and parietal regions (psychosis with Parkinson's disease); (4) meningioma of the right occipitoparietal region (psychosis due to chronic alcoholism); (5) ependymoma of the optic chiasm (toxic amblyopia); (6) bilateral tumor of the frontal lobe (encephalitis), and (7) neurofibroma of the optic nerve and chiasm (Fröhlich's syndrome).

The authors point out the necessity of diagnosis of brain tumor in patients with psychiatric disorders, especially when the tumor has given rise to the psychiatric signs and when it is operable. The importance of studies by air injection is stressed.

FORSTER, Boston.

LEVEL OF ADRENO-CORTICAL SUBSTANCE IN THE BLOOD DURING HYPOGLYCEMIC TREATMENTS FOR SCHIZOPHRENIA. ESTHER B. TIETZ and SANFORD M. BIRNBAUM, Am. J. Psychiat. **99**:75 (July) 1942.

Tietz and Birnbaum studied quantitatively the adrenocortical substance in the blood of 29 patients during the course of insulin therapy. The determination was by colorimetric method, a modification of Shaw's technic being used. Plotting of the preinsulin and coma levels revealed several types of responses. For 4 patients there was a rise in the base line, so that the preinsulin levels were definitely increased. These patients recovered. Four patients revealed decreases in the preinsulin levels; these patients failed to recover. Of 11 patients who maintained low preinsulin levels but near the end of treatment showed increments during coma, none made a complete recovery. Tietz and Birnbaum conclude that a correlation exists between clinical recovery and changes in the levels of adrenocortical substance in the blood during insulin therapy.

FORSTER, Boston.

ANALYSIS OF CERTAIN FACTORS IN HISTORIES OF TWO HUNDRED SOLDIERS DISCHARGED FROM THE ARMY FOR NEUROPSYCHIATRIC DISABILITIES. SEYMOUR J. ROSENBERG and RICHARD H. LAMBERT, Am. J. Psychiat. **99**:164 (Sept.) 1942.

Rosenberg and Lambert reviewed the cases of 200 soldiers discharged from the Army for neuropsychiatric disabilities. All occurred in a training camp in the United States. The majority of the men had not been in the service more than three months. One half of the disabilities were for psychoneuroses, one third for psychoses and one sixth for epilepsy. In the group of patients with psychoneuroses the entities in the order of frequency were hypochondriasis, hysteria, anxiety states, mixed neuroses and neurasthenia. Cases of dementia praecox constituted the vast majority of the psychoses.

Rosenberg and Lambert found the reaction types similar to those of civilian life. Frequently the psychoneurotic reaction displayed by a person in the service was similar to his lifelong behavior pattern. While the men with neurotic reactions adjusted poorly to the service, men with epilepsy made satisfactory soldiers and desired to remain in the service. Eighty-two and a half per cent of the 200 patients had presented symptoms for at least one year prior to induction. Of the 22 men with onset after induction, all but 1 were psychotic.

Almost one-half the total number were disabled within one month of service, and 97 per cent, after six months. Rosenberg and Lambert point out the role of psychiatrists on the induction board in preventing the acceptance of men with neuropsychiatric disorders.

FORSTER, Boston.

BRAIN INJURY, DRUGS AND ENVIRONMENT AS CAUSES OF MENTAL DECAY IN EPILEPSY. WILLIAM G. LENNOX, Am. J. Psychiat. **99**:174 (Sept.) 1942.

Lennox gathered data on 1,905 patients with epilepsy, 449 of whom were considered to have the "symptomatic" and the rest the "essential" type. The data were reviewed to determine the roles of injury to the brain, drugs and environment as causes of mental deterioration. In determination of the role of injury to the brain it was difficult to say whether deterioration was a result of the injury itself, of the seizures or of both. Comparison of patients with a history of cerebral trauma prior to the onset of seizures and of patients without such a history revealed that deterioration was more common in persons with cerebral trauma and that trauma was a more prominent cause if it occurred before or at birth. The poorer mentality of patients with symptomatic epilepsy could be explained in part by the earlier onset of seizures in this group. The relatively poor mentality of patients with this type of epilepsy occurred in spite of their having fewer seizures.

In studying the effect of medication, Lennox found that phenobarbital improved the seizures of 65 per cent and the mentality of 30 per cent, while the corresponding figures for bromides were 53 and 26 per cent and for patent drugs 40 and 13 per cent. The hypnotic drugs are those accused of contributing to the deterioration. Lennox believes that environmental factors contribute only by augmentation of other factors in the development of deterioration in epilepsy. He concludes that of the three factors discussed, a pathologic process in the brain is the most important etiologically, but from the point of view of therapy, overmedication is the most important factor to be considered.

FORSTER, Boston.

FURTHER FOLLOW-UP STUDIES IN INSULIN-SHOCK THERAPY. E. D. BOND and T. D. RIVERS, Am. J. Psychiat. **99**:201 (Sept.) 1942.

Bond and Rivers compare the rate of recovery from schizophrenia following insulin therapy with the spontaneous recovery rate derived from the same institution, the same diagnostic criteria being employed in the two groups. They found following insulin therapy an immediate recovery rate of 55 per cent, which showed a tendency to level off during the second, third and fourth years at about 33 per cent. The immediate recovery rate following therapy was five times the spontaneous rate, while the long time rate was about twice the spontaneous rate. Bond and Rivers point out that not only is the recovery rate higher after therapy but the results are achieved in a shorter time.

FORSTER, Boston.

AN UNUSUAL CASE OF PROLONGED COMA IN HYPOGLYCEMIC SHOCK TREATMENT. L. D. PROCTOR and N. L. EASTON, Am. J. Psychiat. **99**:203 (Sept.) 1942.

Proctor and Easton report the case of a woman aged 29 with a schizoaffective psychosis who was treated with insulin shock. At her twenty-ninth treatment she was given 220 units of insulin and went into her seventh insulin coma. After an hour unsuccessful attempts were made to terminate the coma by the administration of dextrose and sucrose. A half-hour later the patient was moribund, emergency shock procedures were instituted, and thiamine chloride was given intravenously. Pulmonary edema and hyperthermia (103 F.) complicated the picture. Twelve hours after inception of the coma the patient was in light first stage anesthesia. After three days antishock measures were no longer needed. On the second day the patient first attempted to speak. Lumbar puncture on the third day revealed increased pressure and moderate pleocytosis. On the thirty-sixth day after the onset of coma she had returned to her previous level. The blood sugar level varied between 48 and 320 mg. per hundred cubic centimeters. Proctor and Easton, on the basis of dextrose tolerance curves taken before and after the insulin therapy, believe that their patient presented an abnormality of carbohydrate metabolism.

FORSTER, Boston.

THE PSYCHIATRIC ASPECTS OF MARIHUANA INTOXICATION. SAMUEL ALLENTUCK and KARL M. BOWMAN, Am. J. Psychiat. **99**:248 (Sept.) 1942.

Allentuck and Bowman studied the effects of marihuana on 77 subjects. They point out that the physiologic effects of the drug are similar to those of the atropine series, while the psychic effects are like those of alcohol. Physiologic effects include reddening of the conjunctiva, dilatation of the pupils, photophobia, lacrimation, nystagmus, tremors of the eyelids and extremities, parching of the throat, increase in pulse rate, rise in blood pressure, twitching, hyperreflexia and hypersensitivity in the usual modalities. Psychic manifestations consist of euphoria, volubility and increased psychomotor activity, followed by lassitude, hunger, fatigue, sleepiness and, on arousing, a "hang-over." Under the effect of the drug there are no abnormalities of mental content, and but slight lowering of the intellectual capacities. A psychosis may be precipitated in an unstable person. This occurred in 9 of the 77 subjects. The psychosis is not pathognomonic, but is dependent on the personality and the mood of the patient. It can be controlled by withdrawal of the drug and the administration of barbiturates. After prolonged use of the drug cessation causes no withdrawal symptoms. Allentuck and Bowman used marihuana in the treatment of withdrawal states in cases of addiction to opiates, and while their results are as yet inconclusive, they suggest that this method may prove efficacious.

FORSTER, Boston.

NEUROTIC EXCORIATIONS. F. E. SENEAR and H. SHELLOW, Arch. Dermat. & Syph. **46**:825 (Dec.) 1942.

Senear and Shellow describe cases of compulsion neurosis associated with self mutilation. In the first case instruments of various sorts were used to remove fancied foreign bodies in the submaxillary region, with the resulting development of a number of scars. In the second case the patient began by using a needle to remove comedos and to open acne pustules on the face. This led to an urge to dig deeper into the tissue of the face, for which scissors and tweezers were used. With these instruments the patient gouged out pieces of skin over an area the size of a silver dollar in some places. Psychiatric treatment in this case was of some help in the treatment of the neurosis.

ALPERS, Philadelphia.

A DEPRESSION-HYPOSEXUAL-ALOPECIA SYNDROME. C. ALLEN and C. CARLYLE-GALL, Brit. M. J. **2**:67 (July 18) 1942.

Allen and Carlyle-Gall report the case of a 33 year old man with complete alopecia, associated with deep depression. All hair-bearing areas except the axillas were denuded.

Lack of sexual interest occurred simultaneously with the alopecia. This was associated with a decrease in or absence of capacity to fulfil the sexual act. The authors call attention to the similarity of the condition in their case to Simmond's disease. Although they do not attempt to explain the cause of the syndrome, they suggest the possibility of an endocrine origin. However, they state, the cause of the damage to the glands is yet to be determined.

ECHOLS, New Orleans.

Diseases of the Brain

AN ANALYSIS OF THE DISTURBANCES OF THE HIGHER CORTICAL FUNCTIONS, AGNOSIA, APRAXIA AND APHASIA. HARRY A. TEITELBAUM, J. Nerv. & Ment. Dis. **97**:44 (Jan.) 1943.

Teitelbaum classifies cortical functions under three levels on the basis of their increasing complexity. In the sensory sphere these functions are (1) ability to be aware of primary sensations, (2) ability to recognize the various agents and symbols which give rise to primary sensations and (3) ability to understand the significance and meaning of these agents and symbols. The levels of motor function are represented by (1) ability to contract striated muscle voluntarily, (2) ability to perform purposeful movements and (3) ability to produce meaningful language. With each sphere are associated defects corresponding to each of the levels—anesthesia, agnosia and sensory aphasia, on the sensory side, and paralysis, apraxia and motor aphasia, on the motor side.

Agnosia is difficult to distinguish from sensory aphasia and is often combined with it. Agnosia may be arbitrarily divided into seven types: Body agnosia is inability to recognize the various parts of the body, the patient's or some one else's, and is due to impairment of the cortical mechanism for recognition of the body image. Spatial agnosia refers to inability to recognize the relative positions of the various parts of the body to one another, their positions or the position of the body as a whole in space and the relative positions of various objects to each other in space. Disorientation for right and left and inability to recognize geometric figures are included in this category. Temporal agnosia is a state of faulty orientation for time, with inability to estimate short intervals. Object agnosia is inability to recognize common objects with either one or several senses. Symbolic agnosia is inability to recognize words, numbers, music or gestures as symbols. By some a specific picture agnosia is differentiated from the general group of object agnosias. Inability to recognize colors (color agnosia) must be differentiated from difficulty in naming colors due to aphasia.

Sensory aphasia consists of a disturbance in ability to understand the meaning of symbolic expressions, such as language, numbers and music, not due to primary sensory defects, agnosia or mental deficiency. An important form of this is language aphasia, or inability to understand the meaning of words, phrases and sentences, either written or spoken. Patients with this defect often have paraphasia and jargon aphasia and may display alexia or visual aphasia. Number aphasia is not fundamentally different from language aphasia. It includes acalculia, or inability to use arithmetically numbers that can be understood when read or heard. Music aphasia (amusia) has been divided by Henschen into motor and sensory varieties. It may occur independently of language and number aphasia. Agraphia, when not an apraxic defect, may be due to spatial agnosia.

Apraxia is divided into three basic forms: kinetic apraxia of the limbs, ideokinetic apraxia and ideational apraxia. In motor, or Broca's, aphasia, the patient knows what he wants to say and understands spoken or written language, but is unable to express himself.

CHODOFF, M. C., A. U. S.

UNUSUAL SYMPTOMATOLOGY WITH TUMORS OF THE CEREBELLUM BASED ON ONE HUNDRED AND FIFTY-EIGHT VERIFIED CASES. FRANCIS C. GRANT, JOHN E. WEBSTER and LAURENCE M. WEINBERGER, Am. J. M. Sc. **202**:313 (Sept.) 1941.

Grant, Webster and Weinberger analyzed 158 cases of verified tumor of the cerebellum in an endeavor to call attention to unusual cerebellar symptoms and signs and thus to clarify the diagnosis in the atypical case. A summary of their observations reveals that motor convulsions were present in 21 cases and attacks of loss of consciousness in 13 cases, a total of 34 cases of the convulsive state, or a percentage of 21.5. The convulsions ranged from syncopal attacks, at one end of the "convulsive spectrum," to tonic fits, at the other. The tonic cerebellar fit was described as a decortication, rather than as a decerebration, phenomenon. The occurrence of various types of convulsions may be accounted for on the basis of changes in cerebral blood flow. Significant and confusing alterations in the visual fields were present in 8 cases. It is believed that the distended third ventricle may have produced these defects. Papilledema was present in 126 instances and absent in 15 instances. In the remaining 17

cases the sign was not recorded or was equivocal. The complaint of impaired or failing vision was present in 50 per cent of cases. In 6 cases this complaint was present in the absence of papilledema. Transient attacks of blindness occurred in 5 cases. In 8 cases, in which the patients had visual hallucinations there was concomitant impairment of vision. In no instance could localizing significance be attached to the complexity of the hallucinations. In the majority of cases nystagmus was present. In 41 instances, however, this sign was absent. Lumbar puncture was performed without untoward results in 50 cases of tumor of the cerebellum. In 11 of these cases the spinal fluid pressure was within normal limits (100 to 200 mm. of water).

In one third of 108 cases in which a roentgenologic study was made, there was evidence of increased intracranial pressure. In 21 of 37 cases in which ventriculographic tests were performed, internal hydrocephalus was observed. Numbness of the face, which was present in 8 instances, was probably a result of increased pressure. In 14 cases the caloric test failed to indicate the presence of tumor in the posterior fossa, which was subsequently encountered.

The tendon reflexes were normal in the majority of cases, and in 17 instances palsy of the facial muscles was reported. Deafness or impaired hearing was present in 28 cases and tinnitus in 29 cases. In 4 cases the syndrome of the cerebellopontile angle, with palsies of the fifth, seventh and eighth cranial nerves, was presented.

MICHAELS, Boston.

OCULAR SIGNS OF INTRACRANIAL SACCULAR ANEURYSMS. FRANK B. WALSH and ARTHUR B. KING, Arch. Ophth. **27**:1 (Jan.) 1942.

Walsh and King report 31 cases of saccular aneurysm, with their basic ocular symptoms. Saccular aneurysms are subdivided into miliary aneurysms, the result of atheromatous changes in older persons; mycotic aneurysms; post-traumatic aneurysms; atheromatous aneurysms in the circle of Willis, and congenital, or "berry," aneurysms, the result of congenital deficiency in the walls of the cerebral vessels at their bifurcations.

The topical diagnosis of saccular aneurysm seems to depend on the following cardinal points: (*a*) neighborhood signs, such as paralysis of the oculomotor nerve or pressure on the optic nerve, the chiasm or the tracts; (*b*) the presence of subarachnoid hemorrhage, and (*c*) signs of disease which might produce an aneurysm, such as infective endocarditis or arteriosclerosis, and a history indicating previous subarachnoid hemorrhage, together with signs of tumor at the base of the brain.

The authors report cases illustrating aneurysms accounting for unilateral defects of vision; aneurysms accounting for bitemporal field defects; aneurysms not usually attended by loss of vision, such as intracavernous aneurysm; aneurysmal involvement of the optic tracts, resulting in incongruous hemianopia, and posterior aneurysms accounting for ocular signs and simulating cerebellar neoplasms.

The authors describe ocular signs hitherto not described in association with saccular aneurysms which depend on regeneration of oculomotor nerve fibers. The syndrome has long been known as the pseudo-Graefe phenomenon. A second pseudomotor and pupillary phenomenon was observed, which the authors speak of as the denervation phenomenon. Apparently, this depends on Cannon's law of denervation. Cannon stated that "postganglionic and, to a lesser degree, preganglionic section of any nerve results in increased sensitivity of the innervated structure to the chemical mediator, whether that mediator is sympathin or acetylcholine. The sensitivity persists providing that regeneration does not occur and that the innervated structure does not become atrophic."

The sign appeared in the authors' patient as an elevation of his lid, which invariably appeared when he lost his temper or became interested in an attractive member of the opposite sex.

The experimental studies were carried out on adult human beings, all of whom had died at least five days before. In each of the four experiments, Dandy's "trap" operation was used to show roentgenographically and microscopically the filling of the ocular arteries by way of the external carotid circulation.

SPAETH, Philadelphia.

THE QUADRILATERAL SPACE OF MARIE. J. M. NIELSEN and ARNOLD P. FRIEDMAN, Bull. Los Angeles Neurol. Soc. **7**:131 (Sept.) 1942.

Nielsen and Friedman report several personally observed cases and review recorded cases of lesions involving the quadrilateral space of Marie. The material presented shows that within this space the external capsule has much to do with language by virtue of its conveying of impulses from the language-forming area to Broca's convolution. Destruction of this area causes either motor aphasia and agraphia or paraphasia and agraphia. The para-

graphia is due either to faulty formulation in the posterior language formulation area or to faulty execution in Broca's area.

Destructive lesions of the external capsule require the patient to use the speech mechanism of the minor hemisphere as a unit or to perform one of two functions (formulation or emission) on the minor side and the other on the major side. Utilization of the minor area of Broca results in motor aphasia until time is available for training. Utilization of the minor area of formulation results in the conveyance of impulses across the corpus callosum or the major convolution of Broca, as a result of which paraphasia occurs. Destruction of the anterior limb of the major internal capsule produces dysarthria or anarthria by interruption of the projection of the fiber tracts from the precentral gyrus to the pons and the medulla. Such a disturbance has no relation to aphasia.

LESKO, Bridgeport, Conn.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

CHARLES DAVISON, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding*

Joint Meeting, Feb. 9, 1943

The Neural Mechanism of Paralysis Agitans. DR. ROLAND M. KLEMME, St. Louis (by invitation).

By means of sections taken after excision of the premotor cortex, from the cortex, the corpus callosum, the insular cortex, the superior lentiform nucleus, the internal capsule at the genu, the midbrain, the pons and two levels of the medulla, fiber tracts from the premotor cortex were traced to the spinal cord. With the evidence presented, the mechanism of the tremor of paralysis agitans is projected.

The concept of the mechanism is that of an asynchronicity of the efferent impulses from the basal ganglia and the premotor area impinging on the common path cell complex in the cord. The functional interrelation of the basal ganglia and the premotor cortex must be in balance, the two structures exerting their influence on the common path cell for normal behavior. The intact complex maintains tone. Lesions of the basal ganglia (substantia nigra and globus pallidus) produce an asynchronicity of impulses at the common pathway cell complex—hence tremor.

Removal of the normal premotor cortex, in the absence of the normal influence of the basal ganglia, abolishes the asynchronicity and hence the tremor at rest. Excision of the premotor cortex interrupts the premotor fibers at their source.

Modification of Spastic Hemiplegia by Cortical Excision. DR. E. JEFFERSON BROWDER, Brooklyn.

No attempt is made in this communication systematically to review the recorded observations on the changes in sensation and motor performance that result from destruction of the sensory cortex. It is well established that ablation of this area of the brain in monkeys is followed by alterations in both the tactile and the proprioceptive components of sensation and by disturbances in motor performance on the contralateral side. In man, a variety of pathologic lesions of the parietal cortex have been known to accompany deficits in sensory and motor function. The state of the implicated skeletal muscles associated with a lesion so placed has been termed hypotonia by Head, decreased resistance to passive movement by the New Haven school of neurophysiologists and flaccidity by most clinicians.

A year ago a presentation before the New York Neurological Society by Dr. Benjamin Balser (Spastic and Flaccid Hemiplegia of Cerebral Origin, ARCH. NEUROL. & PSYCHIAT. **48**:340 [Aug.] 1942) evoked discussion of the major features of these variations. Briefly stated, motor hemiplegia is associated with spasticity of the skeletal muscles; sensory hemiplegia, with relative flaccidity, and the mixed type of hemiplegia, with variable alterations in resistance to passive movements. The question here is: Will spastic hemiplegia of cerebral origin be modified by ablation of the parietal cortex on the side of the cerebral lesion? Only scant experimental work on this problem has been recorded. Fulton, in his "Physiology of the Nervous System" (New York, Oxford University Press, 1938), stated: "In unpublished studies, Walker finds that primary ablation of the post-central gyrus in the chimpanzee causes no spasticity. If, however, it is associated with a lesion entirely confined to area 4, a severe spasticity, most marked in the distal muscles group, is present. This is much greater than that seen with an isolated lesion of area 4." This does not take into account the effects produced by lesions of areas 6 and 4s, both of which seldom escape impairment of function after cerebral hemorrhage or arterial occlusion. Be that as it may, it has been repeatedly observed that enduring flaccidity of the hemiplegic side, in cases of disease of the cerebral arteries in particular, not infrequently accompanies demonstrable sensory changes on the involved side. It seems logical, therefore, to assume that so-called motor hemiplegia with associated spasticity of the implicated extremities would be favorably modified if converted into a mixed type by removal of a part of the parietal cortex.

The results of excision of parts of the parietal cortex in 3 cases are presented. Operation was performed in case 1 in an attempt to arrest recurring convulsive seizures. Spasticity of a withered left hand and forearm was considerably relieved. The patient was followed for only two months, during which period improvement in function of the hand continued. In case 2 a planned excision of almost the entire right parietal cortex was carried out in an attempt to modify extreme spasticity of the upper and the lower extremities on the left side. A satisfactory result was obtained, and this has endured for ten months. In case 3, in which the right hand and forearm were severely spastic and the lower extremity was much less so, there were, as in case 1, recurring convulsive seizures. Surgical excision of atrophic cortex from the left parietal region (parts of areas 5 and 7) was not followed by any demonstrable change in the spastic hand.

Conclusion.—From this limited experience no definite conclusions are drawn. The results open up a new field of endeavor, from which useful therapeutic measures may be evolved. Selected patients with hemiplegia accompanied by severe spasticity may be made ambulatory. It is proposed that other patients with enduring flaccidity may be helped by excision of part of the precentral cortex.

In case 2 a relatively large area of cortex was removed. In addition to other effects, complete relief of pain in the left shoulder associated with movement of the arm was obtained. Consideration should be given to the possibility of excision of the parietal cortex for relief of the discomforts accompanying the thalamic syndrome. In all instances the patients to be submitted for operation should be carefully selected lest the proposed procedure fall into disrepute before it has been given a fair trial.

DISCUSSION ON PAPERS BY DR. KLEMME AND DR. BROWDER

DR. TRACY J. PUTNAM: It is seldom that one has an opportunity of seeing anatomic preparations of a human brain from which area 6 and 8 have been removed. Dr. Klemme's specimens show clearly that the fibers from area 6 descend through the pyramids in the medulla and are, as far as I can see, really indistinguishable from the rest of the pyramidal tract. They are obviously corticospinal fibers. In the specimens which have been shown the degenerations closely resemble those following corresponding extirpations in other primates.

This fact, taken in connection with the clinical results, which have been rather briefly reported, has provided additional evidence that section of the corticospinal tract at any level of its course modifies alternating tremor. This result can be attained by excisions of the cortex, as Bucy, Klemme and others of us have done. The same thing can be accomplished by section of the anterior limb of the internal capsule, as shown by Meyers and others. Possibly the operation on the ansa lenticularis, described by Meyers, actually interferes with the anterior edge of the corticospinal tract. Finally, the same result can be produced by section of the lateral pyramidal tract in the spinal cord. Section of the anterior column does not relieve alternating tremor.

My own experience leads me to think that the cortical area which must be excised for relief of alternating tremor is area 6, not area 8. The operations which I have performed have all been done with the use of local anesthesia, and excision of the cortex has been preceded by injection of procaine into the cortex, which allows one to outline precisely the area it is necessary to remove. Under these circumstances, it is clear that infiltration of area 8 with procaine does not relieve the tremor. In all my cases the specimens removed consisted solely of area 6. Only a very small piece of tissue needs to be removed in order to relieve the tremor—sometimes as little as 2 Gm., never more than 5 Gm. There appear to be lower morbidity and mortality rates after such conservative removals than after the more radical extirpations reported by Dr. Klemme. So far my colleagues and I have had no deaths. The operation on the cord has certain advantages; no tissue is sacrificed, and I think that sometimes the hand is more useful. Concerning the clinical facts there can be only agreement. How can they be interpreted? That some kind of a rhythmic circuit is involved in alternating tremor is extremely likely. This was intimated by Hughlings Jackson, and the concept has become clearer and clearer with time. Most recent investigators, for example, Hoefer, Meyers and Bucy, have accepted this theory. The question, however, is: Where is this circuit? As I understand it, Dr. Klemme believes that the corticospinal tract descending through the pyramids is one arc of this rhythmic circuit, and this is an attractive hypothesis. There are one or two objections to the idea, however, which have caused Dr. Hoefer and me to abandon it. First, section of the posterior roots or the posterior columns, the operations of Foerster, Davis and Puusepp, does not abolish tremor; so it is hard to see how the afferent impulses can get back to the cortex. Second, no rhythmic discharge has ever been elicited from the scalp or from the cortex at the time of operation, and it seems that one ought to find such a discharge if the tract were a part of the circuit. So one is faced with a paradox.

for which I do not have a solution, and I hope Dr. Klemme will comment on it. I should like also to ask him why he believes that the fibers from area 6 travel in the direct, and not in the lateral, pyramidal tract and in what sense he uses the term "internuncial fibers."

I wish I had had more experience with which I could compare Dr. Browder's extremely significant results. I can only add I agree that this study opens a real opportunity for further work and that one should be most cautious, in the selection of patients, not to use those with actual contractures, for whom there could be little outlook for improvement. It seems to me that Dr. Browder's concept rests on a reasonable physiologic basis.

DR. SAMUEL BROCK: Dr. Putnam's illuminating comments have made my discussion much simpler.

First, with regard to Dr. Klemme's paper, which was interesting and provocative: He has traced a descending extrapyramidal tract from cortical area 6, and possibly area 8, to the anterior horn cells of the opposite half of the cord, and he seems to have shown that removal of the cortical origins of this tract causes suppression of the tremor in cases of paralysis agitans; further, he thinks the beneficial effects of the various operations of Meyers, Putnam and Bucy are most likely due to destruction of this pathway. This is a plausible point of view. My interest in this matter is highly theoretic. I find it difficult to follow his explanation of the mechanism of the tremor as he elaborates it in terms of a disturbance of the basal ganglia which produces asynchronicity of impulses impinging on the common pathway cell complex, but, then, this is one of the hardest nuts to crack in all neurophysiology. I should like to ask Dr. Klemme if he has any proof that the asynchronous volley of impulses impinging on the common pathway cell complex is the cause of the tremor, and that removal of the asynchronicity of this internuncial volley abolishes the tremor at rest. In other words, is this merely a fascinating theory, or has it some neurophysiologic basis? Perhaps Dr. Klemme's explanation is correct. It has the virtue of explaining tremor in terms of an imbalanced, low motor mechanism, on which both cortical (premotor) and pallidofugal, and perhaps nigrofugal, impulses play. Is Dr. Klemme able to invoke the same explanation to account for tremors associated with lesions of the midbrain? Whether or not these questions can be answered is not as important as the fact that neurosurgeons are becoming human neurophysiologists and are making great strides in practical therapy. Under such circumstances theory may well lag behind until the future permits better integration of the bits of knowledge now possessed.

I shall have less to say with regard to Dr. Browder's stimulating paper, but it, again, demonstrates the neurophysiologic approach in human neurosurgery. Again, practical results speed far ahead of theoretic understanding. The fact that a parietal lesion produces a flaccid limb in cases of cerebral paralysis shows that current explanations of cerebral spasticity in terms of subcortical release—that is, as a form of decerebrate rigidity—are inadequate. Apparently, the neural circuits subserving maintenance of tonus are far flung and take in wider, multiple afferent arcs than those usually stressed, i. e., the proprioceptive pathways. Again, I am sure the future will bring forth more and more informative data, which will permit theory to catch up with practice. These two interesting papers have demonstrated how neurosurgery makes effective use of neurophysiology.

DR. CHARLES DAVISON: With regard to Dr. Browder's paper, when Fulton and his associates (Kennard, M. A., and Fulton, J. F.: *Brain* **56**:213, 1933) published the results of their experimental work on spasticity and flaccidity accompanying premotor and motor lesions, Bieber and I (The Premotor Area: Its Relation to Spasticity and Flaccidity in Man, ARCH. NEUROL. & PSYCHIAT. **32**:963 [Nov.] 1934) studied a number of cases of flaccidity and observed in some instances, in addition to involvement of the premotor and motor cortex, lesions of the parietal lobe. The fact that hemiplegia may be flaccid because of involvement of the parietal lobe or of the sensory pathway was well known clinically. In further investigation of this problem, I found a large number of cases of flaccid hemiplegia with lesions in the parietal cortex or of the sensory pathways, anywhere along their course—the thalamus, the pons or the medulla oblongata or even the spinal cord. I believe Dr. Browder has shown conclusively that at least in some cases the parietal lobe plays a role in the production of flaccid hemiplegia.

DR. ROLAND M. KLEMME, St. Louis: I thank Dr. Putnam and Dr. Brock for their discussions. Fifteen minutes, unfortunately, will not permit my going into details. Theoretically, as I tried to emphasize in my paper, it is difficult for me to conceive of inhibitory efferent impulses, as well as of efferent impulses in one area of the brain being transferred to another area of the cortex and then becoming inhibitory impulses, without a more adequate explanation of the mechanism. I think one loses sight of the common path cell complex and the relationship of the impulses to that complex. I hope (as I stated before, this is a preliminary report) that this projection will answer some of the questions. When the substantia nigra and the

globus pallidus, which are accepted areas of degeneration of the brain in paralysis agitans, no longer function normally, in the presence of a normal premotor area, there is asynchronicity of impulses impinging on the common path cell complex; so if synchronicity can be established in that cell complex by removal of the counterbalance, that is, the premotor cortex, balance is reestablished. I have not finished making all my sections of the specimens, and I hope later to be able to answer some of the questions a little more fully; however, I have clinical evidence that interruption of the premotor area, whether in the spinal cord, at the caudate nucleus, in the internal capsule or in the cortex of the brain, influences the tremor and spasticity. This paper is a projection of an idea by no means fully proved.

With respect to the effect on the internuncial fibers, the work of some of my colleagues in St. Louis on the quantitative estimation of the impulses impinging on the common path, an error of about 5 per cent being allowed, showed that the impulses from the motor cortex constitute about 6 per cent, while those from the premotor cortex make up about 10 per cent. The internuncial fibers contribute about 70 per cent.

Again, let me emphasize that this report is a projection of the mechanism for paralysis agitans, and I hope that in the next eighteen months my associates and I shall be able to obtain definite evidence not only of the connection between the premotor bundle and the thalamus, but of the structures beneath the substantia nigra, the globus pallidus, some areas in the medulla and one area in the pons.

I, again, want to thank the discussers of my paper for the excellent consideration they have given me.

DR. JEFFERSON BROWDER, Brooklyn: I have nothing to add to what I said regarding ablation of the parietal cortex, but I should like to make a few comments on some of the work done by one of my associates, Dr. H. Russell Meyers, up to October, 1942, when he reported for military duty. Some two and a half years ago he presented before this society (Meyers, H. Russell: Surgical Procedure for Postencephalitic Tremor, with Note on Physiology of Motor Fibers, ARCH. NEUROL. & PSYCHIAT. **44**:455 [Aug.] 1940) the results in a patient of excision of the head of the caudate nucleus with undercutting of the premotor area. A cinematographic presentation of the patient showed striking cessation of the alternating tremor. Early in November 1942, when the patient reported for examination, there had been a return of the tremor, which was in every respect similar to that present prior to operation. This seems to lend support to what Dr. Klemme and Dr. Putnam have said. In other cases Meyers has sectioned the anterior half of the anterior limb of the capsule, and this, too, has produced cessation of tremor. It has also resulted in rather considerable transitory and slight residual paralysis in some cases. I believe that the results of excision of the head of the caudate nucleus may be explained merely as a disturbance of the arterial blood supply of the capsule at that site. Division of the ansa and the fasciculus lenticularis, as devised by Meyers and carried out in 9 cases, has given the best results of any operation we have performed. The mortality, 4 out of 9 cases, was, however, too high to permit us to offer this procedure to the public. Consequently, it had been planned before he left to discontinue this particular procedure. Of all the operations used—excision of the premotor cortex, undercutting of the cortex, division of the anterior half of the anterior limb of the capsule and section of the pallidofugal fibers—the safest and best results have been obtained, I believe, with section of the capsule, as described. I have been much interested in Dr. Klemme's explanation of alternating tremor. It is a fascinating one. As he says, I do not believe the projected mechanism is nearly proved as yet, but it is to be hoped that in another eighteen months he will have the answer.

Endopsychic Factors in Causation of Traumatic Neurosis. DR. SÁNDOR LORAND.

Material was presented from 2 cases in which psychoanalysis was used to show the importance of the pretraumatic personality in the development of war neuroses. In fact, the patients presented did not have war neuroses but manifested symptoms at the onset of the war similar to those of the traumatic war neurosis. They showed marked regression and revealed the tendency to escape in illness, with production of many and varied new symptoms which were closely related to the threat of war, which they conceived of as a threat of annihilation to themselves.

Psychiatric Reactions to the War as Seen in Civilians and Soldiers Referred to a Mental Disease Hospital. DR. CURTIS T. PROUT, White Plains, N. Y.

A review of the records of patients admitted to the men's service of the New York Hospital, Westchester Division, revealed that between the invasion of Poland, on Sept. 1, 1939 and Jan. 1, 1943, 41 men had been received in whom various precipitating factors associated with the war had resulted in psychiatric reactions requiring care and treatment in a hospital.

These disturbances were divided into (1) reactions directly due to military service, either prior or subsequent to induction, and (2) civilian reactions due to occupational stress, presence in the war zone, news of the bombing of Pearl Harbor, religious conflicts, sensitiveness over foreign descent and the induction of members of the family.

The majority of these reactions were in the affective sphere. Fifteen men presented a depressive mood; 13 manifested hyperactivity or elation, and 10 were suicidal. Anxieties, efforts at escape, panic states and paranoid trends followed, in 5 patients each. The psychiatric symptom complexes offered no new problems and were indistinguishable from those observed in peacetime. There was a high incidence of familial nervous or mental illness, revealing a hereditary predisposition to mental illness.

DISCUSSION ON PAPERS BY DR. LORAND AND DR. PROUT

DR. A. A. BRILL: Both these papers are interesting and to the point; neither gives anything particularly new. One finds similar cases in peacetime, as well as during war. In Dr. Lorand's cases the condition was not a traumatic neurosis in the neurologic sense; he means that the men's trauma resulted from the knowledge that they might be drafted. Such a neurosis may be called traumatic, particularly the psychoneurosis. In Dr. Prout's cases, as he himself states, the reactions were similar to those in peacetime. These papers have amply demonstrated what I have long believed, and have expressed on many occasions—there are no special traumatic war neuroses. I cannot understand why so much fuss is made about war neuroses and psychoses. However, the so-called war neuroses are not always like the conditions described this evening. In a previous communication I stated that I saw men with latent schizophrenia or mania, as well as many psychoneurotic persons, who went through the first World War and did well. I have already seen men with similar conditions in this war. I have no doubt that there are thousands of psychoneurotic persons in the armed forces, and, as I previously stated, many neurotic men make good solders. I have been interested in the subject since World War I, through my connection with the veterans administration facilities and the study of a number of private patients. I cannot even agree with Freud, who, in his distinction between war and peace neuroses, stated that in the former, in addition to involvement of object libido, the ego is affected. I have seen many traumatic neuroses in peacetime in which the ego was profoundly involved.

Dr. Lorand and Dr. Prout deserve much credit for having shown that the influences exerted by the war on neurotic and psychotic persons are superficial. Dr. Prout's psychotic patients were fundamentally in no way different from civilian patients of the same type. Dr. Lorand's patients merely showed that the war scene acted as a determinant in bringing to the surface already existing hostility and aggression.

DR. ERNST KRIS (by invitation): These two interesting papers have dealt with war as a social situation to which man reacts. The situation is complex, and so is the reaction. Both papers concur in one point: They both assert, in the words of one of the authors, that "the war situation acts as a trigger to psychologic reactions." Dr. Prout's detailed presentation confirms the observations which in the early, "phoney," months of the war were prevalent both in England and in Germany. Dr. Lorand stresses one particular aspect of the situation of "being at war": the existence of aggressive tendencies in a world in which violence has become lawful, the very presence of which is likely to upset the balance of repressions.

The special interest of both Dr. Lorand's cases lies in the fact that in both instances treatment had been started prior to the change in environmental conditions; the histories show that the reactions to the changed environment, to the world at war, fitted into the psychologic structure. In both cases there were produced, so to speak, wartime editions of infantile conflicts. I wish to point out the symbolism in the dreams in Dr. Lorand's first case, in which rifles and guns did not function. The choice of these symbols may be related to the wartime setting; the way in which they were used in the dream indicates the historical background: They refer to that period in the development of the patient in which fear of loss of parts of the body or of their dysfunction—the fears attached to the castration complex—dominates the psychologic scene.

I was personally even more interested in Dr. Lorand's second case, since I have encountered a similar one. The similarity goes so far that even details in the life histories of the two men coincide. Yet there is one decided difference. The young man to whom I refer, a promising British social scientist, came for psychoanalysis ostensibly because of his theoretic interest in Freud's approach to human affairs. He had, however, in reality decided to be treated because of the ever growing pressure under which he lived in the years immediately preceding the present war. A member of the British "squirearchy," he was clearly expected to join the Territorials of his country. The part played in so many wartime neuroses by what is called "the flight into illness" is familiar, and both the papers have touched it. The case I mention was of an opposite kind. The necessity to join the services as soon as possible was

impressed on the young man; yet the psychologic structure in his case was almost identical with that of Dr. Lorand's second case—a beating fantasy, which played so interesting a part in Dr. Lorand's case, prevented my analysand from joining the territorial forces. The content of the fantasy was well defined—that of beating a younger man wearing a uniform. The roots of this typical fantasy were to be found in the patient's early history. During the last war he was from 2 to 6 years of age. His father, a ranking officer in the very regiment the son was supposed to join, came home on frequent visits. The fantasy was developed in a first edition when the child was 4 years of age; it expressed a reversal of the Oedipus fantasy.

I should like now to comment briefly on a more specific point, which both papers discuss: the problem of the pretraumatic personality in "war neurosis" (Eder, M. D.: War Shock, London, W. Heinemann, 1917). I refer not to the classic traumatic neurosis, though Dr. Prout reported a case which might well be included here, but, rather, to the general psychologic reactions to traumatic experience, such as aerial bombardment. The impression of many who have studied the incidence of mental illness in wartime England emphasizes the importance of the pretraumatic personality. Such an impression is, however, difficult to verify. I should like to mention two observations which, so far as I know, have not yet been taken into account in this connection. They were both made without any reference to psychoanalytic theory, and they cannot, therefore, be suspected of favoring the views to be derived from Freud's work.

The first of these observations was presented in a paper by Professor Cyril Burt read before the British Psychological Society on Dec. 20, 1941 (Under Fives in Total War, printed for circulation among members of the society), in which he discussed the reaction of children to the traumatic experience of aerial bombardment. The trauma was defined as the bombing of the house in which the child lived, or of a neighboring house. The intensity of damage was judged by the necessity to evacuate the house during the night or on the following morning. The "pathologic" reaction was defined as any sort of disturbance shown by the child during the week following the bombardment. The results were striking. Few children 2 years of age or less showed any reaction; the incidence was 5 per cent. It has since been learned (Dorothy Burlingham and Anna Freud: Young Children in a Wartime Nursery, London, George Allen & Unwin, Ltd., 1942) that at such an early age the neurotic reaction is due to "contagion"; the child shows the mother's reaction. For children from 2 to 5 years of age the incidence rose to 37 per cent. Unfortunately, Professor Burt's collaborators chose 5, not 6, years, the borderline of latency, as the age limit for this group.

Thirty-seven per cent was the first peak of the curve, which dropped sharply after 5 years of age. For children from 5 to 11 years of age the incidence was 26 per cent. I suspect that had the sixth year been included in the previous group, the drop would have been more pronounced. As one might expect, the trend continued for the next age group; for children from 11 to 14 years of age the incidence was 13 per cent. After the age of 14, however, the trend was suddenly reversed. There was a steep rise between the ages of 14 and 16; 21 per cent of the adolescents of this age showed a "nervous" reaction to bombing.

According to psychonalytic observations, the prelatency age, from 3 to 6 years, is an age of increased tension, and so is puberty, psychologic puberty being delayed in Britain. The curve shows the two peaks at the ages at which this increase in tension may be expected. Professor Burt called his data approximations. I find them highly suggestive.

A second set of data, though less conclusive, deserves to be cited here. It seems to corroborate expectations formulated by psychoanalysts in the last war. In April 1918 Ernest Jones, in a paper read before the Royal Society of Medicine, stated that, according to his impressions, only the men suffered from war neurosis whose "libido, organized on a homosexual, narcissistic basis, was so attached to the ego as to become stimulated when the latter was threatened, i. e., in situations of danger" (Jones, E.: War Shock and the Theory of the Neuroses, in Papers on Psycho-Analysis, ed. 3, Baltimore, William Wood & Company, 1923, chap. 32). For later views expressed by the same author, see "the Psychopathology of Anxiety" (*Brit. J. M. Psychol.* **9**:17 [May] 1929) and "Papers on Psycho-Analysis" (ed. 4, Baltimore, William Wood & Company, 1938, chap. 20).

Dr. Jones's conclusions after World War I were confirmed by investigators in many European and overseas countries, and the impression was repeatedly formulated that latent homosexuality played an important part in the war neuroses of soldiers; similar impressions were published by British observers during the present war (Glover, E.: Notes on the Psychological Effects of War Conditions on the Civilian Population: III. The Blitz, *Internat. J. Psycho-Analysis,* **23**:17, 1942). But the war situation itself affords possibly an opportunity for a more decisive test: In this war soldiers and civilians in Britain have been exposed to the same amount of danger by aerial bombardment. In several discussions I have formulated the expectation that should Jones's hypothesis prove correct, one might well find the incidence of psychopathologic reactions to be higher among soldiers than among civilians. While no absolute figures have yet been released, Dr. Aubrey Lewis, the director

of Maudsley Hospital, London, who was given access to the material, stated that, while the incidence of mental illness under bombardment is not high in the services, it is greater than that in the corresponding civilian population (Lewis, A.: Incidents of Neuroses in England Under War Conditions, *Lancet* **2**:175 [Aug. 15] 1942). This observation can be interpreted in various ways. The civilian population has more opportunities for active participation; the civilian can use his initiative to a higher degree, while the soldier lives under less favorable conditions. But are these conditions not likely to reenforce passive tendencies? Is not the male society of the camps an environment likely to endanger those whom it is customary roughly to qualify as "latent homosexuals"?

To return to the two papers of the evening, they presented macroscopic and microscopic aspects of reactions to the war, aspects which are closely related to each other. The findings of the psychoanalytic microscope are highly suggestive. The pictures are detailed, but they do not allow for quantitative corroboration. It is their function to suggest hypotheses and to point to the essential elements. Macroscopic evidence, on the other hand, blind without the guidance of some constructive "hunches," may well eliminate doubts and verify the observations.

DR. SÁNDOR LORAND: I have not much to say in conclusion. The second patient, who was a fetishist and had latent homosexual tendencies, is now in service. He realized his wish and joined the army in May. When I was informed of it, I crossed my fingers and hoped everything would be all right. He is now overseas and has been in an officers' training school, doing very well. He has not improved much so far as sexual matters are concerned. At the time of his leaving, his sexual gratification was masturbatory. However, since last April he may have had a chance to digest some of the traumatic experiences, the possibility of which analysis compelled him to face.

In the last war men with traumatic shock were given adequate psychotherapy for three or four weeks, after which they were frequently ready to return and fight again. The aim of my presentation was to contrast the facts with the hypotheses and theories about war neuroses. Not much is known about this neurosis. During the first World War I worked fully two years in a hospital and saw hundreds of patients who had been shell-shocked or gassed. From the clinical material I learned the therapeutic approach and the importance of the pretraumatic aspects of the neurosis. The patients presented this evening had a pretraumatic personality; they could have gone on for the rest of their lives with their neurosis because they were not troubled by panic.

The excellent discussion by Dr. Kris was of more value than my paper, and I am especially thankful to him.

CHICAGO NEUROLOGICAL SOCIETY

ARTHUR WEIL, M.D., *President, in the Chair*

Regular Meeting, Feb. 18, 1943

Physique and Character: A Historical Review (Presidential Address). DR. ARTHUR WEIL.

Encephalographic Patterns Associated with Multiple Sclerosis. DR. WALTER FREEMAN, Washington, D. C.

The pneumoencephalogram in cases of multiple sclerosis shows almost as much variation as the clinical or the pathologic picture. In some cases there is pronounced atrophy in the frontal regions, with large collections of air over the cortex and mild to moderate dilatation of the anterior horns of the ventricles, usually asymmetric, although seldom approaching the degree found in cases of presenile dementia. In other instances the atrophy is predominantly in the posterior fossa, although this localization does not always accord with the degree of atrophy of the cerebellum as revealed at necropsy. The presence of focal atrophies in the central convolutions may explain some of the peculiar dissociations of sensibility and of motion.

The electroencephalogram in cases of multiple sclerosis is substantially normal. This was unexpected in view of the pockets of air distributed over the cortex. It is satisfactorily explained, however, on the basis of the known pathologic changes in multiple sclerosis. The lesions shown by air studies are almost certainly not due to atrophy of the cortex but are the result of cicatricial contraction of the subcortical white matter where the characteristic plaques occur.

Pneumoencephalographic and electroencephalographic studies of multiple sclerosis thus serve to present complementary pictures of the disease process and to reveal aspects of the

disease that are in satisfactory harmony both with the clinical characteristics of the disease and with its pathologic anatomy.

DISCUSSION

DR. HAROLD C. VORIS: I am glad to hear that Dr. Freeman does not think that encephalograms are diagnostic in cases of multiple sclerosis. I have never made any except in 2 cases of the early stage of the disease, in which the picture was sufficiently confusing to make one suspect tumor of the brain; in neither case did the encephalogram show anything of note. I have had occasion, particularly at the Cook County Hospital, to make encephalograms of a number of patients with epilepsy of variable duration and of patients with subjective symptoms following trauma to the head. As many know, under such conditions one not infrequently finds more or less pooling of air in the subarachnoid spaces in various parts of the cavity, which I find hard to differentiate from the pictures shown tonight.

Pneumoencephalographic studies are not made unless the patient has some complaint, and I am not sure it is clear what constitute normal variations. How often may one find dilatation of the ventricles in the routine encephalograms of patients who never had any neurologic complaints?

DR. VICTOR E. GONDA: In line with Dr. Voris' comment, I wonder whether any one has something to say about that ever present air shadow in the occipital region.

Dr. Freeman insinuated that it is criminal to give fever therapy in cases of multiple sclerosis. Many others have expressed this opinion. Still, in cases which are complicated by retrobulbar neuritis such remarkable effects on ocular symptoms follow fever therapy that I think it would be criminal not to resort to this type of treatment when such a case presents itself.

DR. CLARENCE A. NEYMANN: Did Dr. Freeman mean that fever therapy is always a criminal procedure or criminal only in the specific case described? Osborne and I were the first, about ten years ago, to treat multiple sclerosis with artificial fever. Ten or more of the original 25 patients, or about 40 per cent, seemed to have been greatly benefited at that time. I have seen many of these patients intermittently since, and it is my impression that most of those who improved after fever therapy now are in about the same condition as they were directly after the treatment. Seemingly, the disease has not progressed much. Not later than last week a patient was reexamined who had been treated at Cook County Psychopathic Hospital in 1932. He is in excellent condition.

DR. A. EARL WALKER: Dr. Freeman has reviewed a controversial subject in an interesting manner. His explanation of the euphoria frequently seen in patients suffering from multiple sclerosis is of great interest. It was formerly thought that this mental state was the result of lesions on the wall of the third ventricle. There was, however, no valid evidence for this assumption, and Dr. Freeman's explanation seems to fall in line with the observations made on patients who have had a prefrontal lobotomy.

It does not seem to me at all surprising that the electroencephalograms of patients suffering from multiple sclerosis show no alterations. It must be remembered that electroencephalography gives only an idea of the activity of groups of nerve cells, not of individual cells, and that while one cell may be firing, its activity may be cancelled by that of another cell that happens to be in a negative stage, so that the electroencephalogram may show no abnormality.

I have seen a number of pneumoencephalograms that appeared similar to those which Dr. Freeman showed. In the majority of cases the patients were suffering from degenerative diseases of the brain. Several were instances of Wilson's disease, and in some the condition was not verified histologically, but it is true that the clinical diagnosis in certain of these cases was multiple sclerosis.

DR. WALTER FREEMAN, Washington, D. C.: In any encephalogram there is a tendency for air to accumulate over the frontal region because the patient goes to the x-ray room lying on his back. If he were lying on his face or sitting upright, one might see a different picture. The subarachnoid spaces are narrow, and air bubbles can trap the liquid easily, and only occasionally can one get a complete picture of the pathways.

In normal subjects I do not think one finds the stellate shadows I pointed out in the encephalograms of patients with multiple sclerosis. I agree with Dr. Gonda that interpretation of shadows in the posterior fossa is difficult, and I should not make a diagnosis of atrophy unless the cerebellar folia showed such atrophy. With a large collection of air in the posterior fossa I think one is justified in making such a diagnosis.

In this particular case fever therapy was unjustified. Malaria therapy was used, and the temperature rose to 107 F. and was allowed to remain high until the patient was paralyzed and had bed sores. I remember twitting Dr. Neymann on fever therapy once; that was with regard to the diathermy treatment of neurosyphilis, which I think has been thoroughly dis-

credited. I am glad to hear that more recent results with hyperthermia and with cabinet therapy have been more successful. I am glad to hear Dr. Neymann's report of steady improvement in patients with multiple sclerosis after fever therapy. It is somewhat dangerous, I believe, but some patients have a rather prolonged period of remission.

Neuro-Optic Myelitis. Dr. Heinz Kohut and Dr. Richard B. Richter.

DISCUSSION

Dr. George B. Hassin: In some cases of so-called neuro-optic myelitis, including the one I studied, changes were present throughout the entire system of the visual fibers, including the cuneus. Such an exclusive and extensive destruction of the visual nerve fibers in the presence of softening of the spinal cord is unique in the field of neuropathology, and for this reason neuro-optic myelitis should be considered a specific morbid entity.

The changes emphasized by the authors in a lower lumbar segment in which both the gray and the white matter were destroyed, are significant. They should be of special interest to Putnam, who identifies multiple sclerosis with neuro-optic myelitis and sees the cause of both in vascular anomalies, such as venous thrombosis. Dr. Walter Freeman, who tonight showed atrophy of the cerebral convolutions with dilatation of the lateral ventricles in cases of multiple sclerosis, is inclined to favor Putnam's view. Yet Kohut and Richter state definitely that no vascular changes were present in their case. The authors used the term "necrosis" for the changes in the spinal cord and the optic nerve. "Softening" would, in my opinion, be a better term. On the whole, the name neuro-optic myelitis, which implies an inflammatory lesion, is improper, a misnomer, as no inflammatory signs are present in this condition. Another interesting observation emphasized by the speakers was pleocytosis. It was evidently secondary to the changes in the spinal cord, the pathologic products of which are discharged into the subarachnoid space, where they produce reactive phenomena in the form of pleocytosis.

Dr. Richard B. Richter: The optic system as a whole was examined in its entirety except for the optic chiasm, which, unfortunately, was lost during preparation of the material. Careful inspection of about 3 cm. of the left optic nerve and the optic tract, lateral geniculate body, optic radiations and visual cortex on both sides revealed no changes other than those described in the optic nerve.

Dr. Hassin appears to be in agreement with us on one important point—that neuro-optic myelitis and multiple sclerosis are not the same disease. But we evidently differ about what neuro-optic myelitis is. The case that Dr. Hassin himself described as an instance of neuro-optic myelitis seems to me to be one of disseminated encephalomyelitis. Like so many of the other pathologic reports on neuro-optic myelitis, his deals with an instance of disseminated focal demyelination and softening.

When Dr. Hassin objects to the use of the term "myelitis" in connection with our cases, he also criticizes himself, for he described under the title "neuro-myelitis optica" a condition which he regarded as belonging to his group of "multiple degenerative softening." Dr. Kohut stated explicitly that we do not regard the process in our cases as a primary infectious one. We have used the term "neuro-optic myelitis" because it is the established one, rather than "neuro-optic myelopathy," which might be better.

I wish to call attention, again, to an extremely interesting feature of these cases, which to our minds is not adequately explained, namely, the almost complete absence of inflammatory reaction in the meninges only a few days after the spinal fluid was observed to contain some 2,000 white cells, mostly polymorphonuclear leukocytes. Neither the source of these cells in a process of this kind nor the lack of meningeal reaction is clear to us.

PHILADELPHIA NEUROLOGICAL SOCIETY

F. H. Lewey, M.D., *Presiding*

Regular Meeting, Feb. 26, 1943

Aura of Taste Preceding Convulsions Associated with a Lesion of the Parietal Operculum: Report of a Case. Dr. Henry A. Shenkin and Dr. Frederic H. Lewey,

The term "uncinate fit" was coined by Hughlings Jackson in 1879 to describe a type of epileptic seizure in which ". . . at onset of paroxysms, a crude sensation of smell or one of taste" was a characteristic feature. The portion of the cerebral cortex held responsible for

the experience of this aura of smell or taste sensation was the basal surface of the temporal lobe—specifically, the hippocampal gyrus and its uncus. Since this time it has been taken for granted that the cortical representation of taste is linked with that of smell.

While all evidence points to the validity of the uncinate localization of the sense of smell, there is no such evidence for such a localization of the sense of taste. In fact, Börnstein has shown that all anatomic and physiologic data point to a cerebral representation of the sense of taste separate from that of the sense of smell and associated with tactile sensibility of the tongue. This would place such an area in the inferior part of the postcentral gyrus, the so-called parietal operculum. Börnstein has published clinical reports and experimental data supporting this theory.

REPORT OF CASE

A man aged 27 was admitted to the neurosurgical service of the Hospital of the University of Pennsylvania on July 30, 1942 with a history of recurrent headaches and easy fatigue for two months. During this period he had four generalized convulsive seizures, each preceded by an aura of a sour-bitter taste, seemingly coming from his stomach and followed by nausea. No associated odors were experienced.

Neurologic examination showed only minimal weakness and increased tendon reflexes of the left extremities. There was no papilledema, but the spinal fluid pressure measured 280 mm. of water. No abnormalities of odor could be detected. The perception of sweetness was absent over the entire left side of the tongue. Bitter and salt substances were normally recognized over the entire tongue.

At operation a congeries of large, enormously engorged vessels was located in the sylvian fissure. The point of greatest dilatation of these vessels was over the lowest portion of the posterior central gyrus.

The significant point in this case was the distinct aura of taste sensation preceding the epileptic seizure, with the subsequent observation of a lesion involving the parietal operculum. There was clearly no associated olfactory sensation. The aura of a taste sensation and distinct inability to recognize sweetness on the side of the tongue contralateral to the lesion enabled us to predict preoperatively the probable location of the focus in the region of the inferior portion of the postcentral gyrus, and operative exploration verified the assumption.

This case is reported in order to draw attention to the localizing value of a gustatory aura and to give additional support to the theory, as advanced by Börnstein, that taste sense is represented in the parietal operculum.

DISCUSSION

Dr. W. S. Börnstein: Dr. Shenkin and Dr. Lewey, by presenting their interesting case, have emphasized the fact that disturbances in taste sensation can lead to the localization of a pathologic process in the cerebral cortex, as do visual or motor disturbances.

The map of the cerebral cortex of man shows the following areas in the neighborhood of the cortical area for taste (area 43): Rostrally adjacent is motor area 6 B, representing feeding activities. Impairment of the contralateral muscles of chewing and increased salivation (as a release phenomenon) were present in all my cases of cortical disturbance of taste. Medially adjacent to area 43 is the sensory trigeminal area for the tongue. Hypesthesia, hypalgesia and pathologically increased coating (i. e., trophic disturbance) of the tongue are characteristic neighborhood signs, all involving in most cases mainly, but not exclusively, the side opposite the cortical focus. Farther medial the walls of the mouth, the lips and the thumb are represented. The motor areas for all these structures lie in front of the sensory region. If the pathologic process is located in the dominant hemisphere, motor aphasia is most frequently part of the syndrome.

The following combination of signs ("syndrome of the central operculum") is, therefore, characteristic of lesions in the neighborhood of the cortical taste area: impairment of chewing and hypersalivation; sensory (and motor) impairment of the tongue, mouth, lips and thumb, and motor aphasia.

Theoretic considerations suggest that all these areas, except that for the thumb, are as closely related to each other functionally as they are anatomically and that the topical relations of the respective cortical areas are based on the functional relations of the peripheral organs: The organs, for example, that are essential for taste are essential for feeding and for speaking. The organs of feeding in mammals provide the basis for speaking in man. If the pathologic process spreads laterally from the cortical taste area, beyond the sylvian fissure, impairment of hearing, as a result of involvement of the lateral edge of the auditory cortex, may be observed. The syndrome of the central operculum enables one to distinguish between lesions in the cortical taste regions and subcortical lesions.

Clinical observations of previous authors and my experiments on the monkey, together with those of Ruch and Walker (not yet published) point to the "arcuate" nucleus as the

thalamic synapsis for taste, medial to the trigeminal synapsis. The synapsis for taste in the medulla oblongata, in the nucleus of the tractus solitarius, is well known and need not be demonstrated here.

The authors reported that in their case of a cortical taste aura only the taste quality of "sweetness" was impaired. Such partial impairment of taste, reported by previous authors and observed also in some of my cases, is of great theoretic interest. In the case of cortical taste aura which I have reported elsewhere all four qualities of taste sense were involved. In initiation of the jacksonian attacks there were hallucinations of taste only on the half of the tongue opposite the side of the lesion.

Close functional relations exist between taste and appetite. One of my patients with severe impairment of his sense of taste had also lost his formerly good appetite, as a result of a bullet wound. He no longer enjoyed eating and even the sight of his formerly favorite food was no longer enticing to him. The phenomenon of "cortical anorexia," together with hypogeusia, persisted until his death, six years after the injury. Attacks of petit mal in the form of loss of appetite occurred in another case.

These 2 observations serve well to illustrate the counterpart of the phenomenon of "morbid hunger," as reported by Fulton and his associates. Of practical importance is the fact that even severe impairment of the sense of taste may remain unnoticed by the patient. In contrast to this 1 of my patients was well aware of fluctuations in his acuity of taste sense, which he ascribed to weather conditions. "In good weather," he said, "I taste everything. In bad, particularly in hazy, weather I cannot taste certain things—for example, whether the food is too salty or too sour, or not enough so." Examination of this patient on a sultry day revealed pronounced hypalgesia and impairment of taste sense on the half (right) of the tongue opposite the side of the lesion. During two examinations on sunny days hypalgesia was only slight (merely a subjective difference between the two sides), and the faculty of taste was found to be good except for pathologic fatigability for taste stimuli over the whole tongue.

Another patient had abolition of the taste sense over the whole tongue as an effect of a unilateral bullet lesion. An attempt to explain this rare phenomenon will be made elsewhere. All the examinations for taste sense were performed with graded stimuli. The authors have presented additional proof that this method provides much more useful results than the usual methods of examination of the sense of taste.

DR. B. J. ALPERS: I wish to ask Dr. Börnstein whether the representation of taste sensation should be regarded as entirely unilateral, or whether it is in any way bilateral.

DR. W. S. BÖRNSTEIN: As a rule taste has bilateral representation, with numerical predominance of the opposite side. There is, however, some variation, as the last case I mentioned demonstrates.

DR. F. H. LEWEY: How is it in animals?

DR. W. S. BÖRNSTEIN: This cannot yet be said, for the right and the left half of the gustatory field in animals have not been compared.

DR. G. P. MCCOUCH: All are intensely interested both in the case presented by Dr. Shenkin and that presented by Dr. Lewey and in the opportunity to hear at first hand Dr. Börnstein's extensive experience in this field.

I have no personal experience in the clinical aspects of this subject, and my only excuse for taking part in the discussion is to raise a point which to a physiologist is rather interesting. A lesion which is primarily postcentral produces an aura and is followed by a jacksonian attack. Why is there no progressive march up the postcentral convolution in the sensory sphere comparable to the march that obtains in the precentral convolution in the motor sphere?

I venture to raise this obvious point because it illustrates a fundamental difference in the patterns of organization of sensory and motor mechanisms. On the sensory side the entire pathway from the receptor to the cortex is a "private" one. This must be so if there are to be collateral reflex connections, the actual sensory pathway must be almost strictly concerned with the particular sensory impulses. Perhaps the only common trespassing is inhibition of one sensation by another.

I do not wish to push the point too far. Of course, it is generally known that there is such a thing as sensory facilitation; yet it is extremely limited. It is seen at its maximum in the experiments of Dusser de Barenne, in which the application of strychnine to a minute point on, for example, the sensory area for the upper extremity gives a sensory spread throughout that area. But there it stops. It never encroaches on the sensory area for the lower extremity or on that for the face. On the other hand, motor mechanisms are built up in their essential structural and functional pattern on the basis of convergence and of facilitation, which is nowhere better exemplified than in a jacksonian attack.

DR. H. A. SHENKIN: The only point I wish to emphasize is the relation of obesity, or rather hyperphagia, to the area for taste.

Dr. Börnstein mentioned this in passing, and I have had occasion to observe experiments at Yale University, in which Drs. Ruch, Patton and I attempted to eliminate the arcuate nucleus in order to check further on this pathway of taste from the cortex to the thalamus. The path was missed often, as any one working on monkeys with the Horsley-Clarke apparatus would appreciate, and the lesions were produced slightly caudal to the nucleus ventralis posteromedialis. Much to our surprise, extremely hyperphagic animals resulted—animals which in two months gained from about 3 to 6 and 7 Kg. in weight, and their diet had to be limited to prevent their death from overeating.

I wonder if it would be possible to link such experiments with hyperphagia observed occasionally with lesions of the frontal lobe and with disturbances of taste, appetite, chewing and sucking movements noted with lesions of the central operculum, as described by Dr. Börnstein.

Pathologic Changes Associated with Metastatic or Embolic Encephalitis. DR. HERBERT S. GASKILL and DR. BERNARD J. ALPERS.

Metastatic encephalitis occurs secondary to infections elsewhere in the body. The source of greatest frequency are the heart valves, particularly in cases of subacute bacterial endocarditis. Acute endocarditis of other types, pulmonary disease and foci involving organs other than the heart and lungs may give rise to this form of encephalitis. The clinical manifestations indicating involvement of the brain, particularly in cases of endocarditis, may usher in the disease; they may be terminal, or they may occur anywhere along its course.

The brain may contain few or numerous areas of metastatic encephalitis. These foci may occur anywhere in the cerebral hemispheres, the brain stem or the basal ganglia. Microscopically, a brain so affected shows: proliferative endarteritis, which tends to be generalized; areas of perivascular infiltration with leukocytes; minute leukocytic nodules, which are essentially miliary abscesses, and, in some instances, areas of petechial and perivascular hemorrhage. Subarachnoid, cerebral or ventricular hemorrhage may be observed, as well as meningitis.

The foci of metastatic encephalitis are probably blood borne and are probably carried by means of the system of paravertebral veins described by Batson.

DISCUSSION

DR. F. H. LEWEY: In Dr. Alpers' cases did there exist a parallelism between the peripheral bacteremia and the appearance of bacteria in the cerebral foci? I am interested in a group of cases in which apparently the relationship is indirect. In other words, endocarditis and articular rheumatism as such produce weakening of the vascular walls, as Dr. Alpers described, and the circulation thus slowed leads secondarily to the collection of bacteria at the site of the primary lesion. These bacteria may be of the same type as the original infection or of another type which was previously latent in the organism.

DR. A. SILVERSTEIN: Has Dr. Alpers any records on the spinal fluid in his cases, particularly in those of pulmonary infection? Did examinations of the spinal fluid show pleocytosis?

DR. G. D. GAMMON: Does Dr. Alpers include cases of acute disseminated lupus erythematosus with encephalitic manifestations in this group? My associates and I have had occasion recently to see some cases of that condition. In 1 instance the original symptom was embolic occlusion of the cerebral vessels as a result of the associated involvement of the heart valves; the cutaneous manifestations of the lupus came on several weeks later.

The other cases we have observed were without definite cardiac involvement, but increased intracranial pressure and papilledema appeared prior to death.

Dr. J. C. YASKIN: Dr. Alpers' paper brings to my mind a fairly large number of cases which my colleagues and I have encountered in recent years. In the first group the cerebral manifestations were associated with subacute bacterial endocarditis. One case has taught me a great deal. It was that of a young man with hemiplegia who was admitted to the Philadelphia Hospital. He was discharged with the diagnosis of hemiplegia of unknown origin. He returned to the hospital about two or three months later with a fulminating type of bacterial endocarditis. I have no doubt that he had carditis on his first admission, when he had a normal temperature and no blood culture was made. It is well known that bacterial endocarditis may exist without any rise in temperature.

I recall another case of a type to which Dr. Alpers did not refer. A young woman was sent to us from Scranton, Pa., with a diagnosis of tumor of the brain. She had fever and petechial spots. There was no difficulty in establishing the diagnosis of subacute bacterial endocarditis. Autopsy showed a large bloody cyst, or a cyst containing sanguineous

fluid, in the right cerebral hemisphere. Has Dr. Alpers actually seen any mycotic aneurysms in his series?

The second group, closely allied to the first, consisted of cases in which cerebral accidents occurred in the course of rheumatic fever. We have encountered several cases within the last two years in which the cerebral accident was the earliest recognized manifestation of rheumatic heart disease. A routine examination failed to disclose the heart disease, but with time the signs became more pronounced. One case was remarkable in that a child of 13 years had sudden left hemiplegia and only after a few months did good evidence of rheumatic heart disease appear.

I am interested in comparing the cases presented by Dr. Alpers with those of frank abscess of the brain. In the third group of cases he mentioned osteomyelitic and intrathoracic suppuration as etiologic factors. This source of metastatic foci in the brain is much the same as the solitary, larger abscess which we have observed.

DR. B. J. ALPERS: Dr. Yaskin brings out an important point—namely, that the symptoms referable to the central nervous system may be the first indication of subacute bacterial endocarditis. I did not emphasize that point because I felt it was well known, but we have had some striking examples of it.

A case of gross cerebral hemorrhage in the present series and a case in Dr. Frazier's laboratory at the University of Pennsylvania are the only 2 instances of mycotic aneurysm associated with endocarditis that I have encountered. Large, solitary, direct abscess may be associated with subacute bacterial endocarditis. It has been reported on a few occasions. It is not common, and I did not include it in this series. I have never seen nor studied cases of acute disseminated lupus; so I do not know what the brain in such cases shows. Were the foci in Dr. Gammon's cases of a type similar to that in our cases? If they were, I should properly have included such cases in this group.

DR. G. D. GAMMON: Pathologic reports on the brains have not yet been finished.

DR. B. J. ALPERS: If I understand Dr. Lewey's question correctly, I do not think there is a parallelism between what goes on in the brain and the course of the infection. There are cases of subacute bacterial endocarditis and cases of severe septicemia without any changes in the brain and cases of subacute bacterial endocarditis with no infection demonstrable by culture in which there is definite cerebral involvement.

Heredofamilial Spastic Paraplegia: Report on a Family. DR. GABRIEL A. SCHWARZ.

A family is reported in which 19 members were known to be afflicted with spastic weakness or paralysis of both lower limbs. Of the 19 afflicted persons, 8 were females. The family was traced through seven generations. The disease was present only in the first six generations. Of the afflicted members, 4 brothers belonging to the fifth generation were examined, and a detailed report on the clinical picture presented by these patients is given.

The ages of onset of the 4 brothers were 45, 8, 34 and 18 years. The duration of the disease was seventeen, forty-four, fifteen and twenty-nine years respectively. The cranial nerves and sensory systems of the 4 patients were normal. Two brothers showed pronounced hyperreflexia of the upper extremities and 2 others slight hyperreflexia. Three of the brothers had spastic paraparesis. One brother had spastic paraplegia. The serologic reactions of the blood of 3 of the brothers were negative. In 1929 the reaction had been reported as strongly positive for 1 of the brothers. This particular patient was treated, and the serologic reaction of the blood became negative and remained so. Examination of the spinal fluid of this brother and of another was negative.

A genealogic analysis of this family showed that the condition was inherited as a dominant trait. There was a "lethal" factor associated with sex which contributed to the peculiar sex distribution of the disease in the fifth generation and suggested the possibility that the dominant character of the disease might be associated with the chromosomal factors for sex. Fewer persons were afflicted in the sixth and seventh generations.

The literature on this subject is considerably confused because a number of conditions have been included under the name heredofamilial spastic paraplegia, for the reason that they presented the single clinical sign of spastic weakness or paralysis of both lower limbs. The family tree and the cases reported here represent a distinct clinical entity. The problems of differential diagnosis and of the pathologic and clinical correlations are discussed briefly.

DISCUSSION

DR. F. H. LEWEY: Am I correct in thinking that the disease was inherited by the females, and only in a single case by a man? The men apparently did not inherit the lethal gene, which would indicate that the heredity of the condition was similar to that of hemophilia.

DR. G. A. SCHWARZ: In the third generation there was 1 man with the disorder, and he had 2 children with the disease.

I thought originally that the transmission was direct and through the females only, but they can have the disease and transmit it, and so can the males, the dominance being, of course, in the females.

DR. S. R. GOVONS: Was the bladder ever affected?

DR. G. A. SCHWARZ: In my 4 patients the bladder was not affected. In 2 of my patients there were minor bladder symptoms, namely, diuresis and frequency of urination for many years. I saw 1 of the patients in the hospital originally for what was thought might be a "cord bladder." Actually he had prostatitis. He has been operated on for that. In the literature there are several cases in which the urinary bladder was affected, but they are not usual.